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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [5] :
C07D 471/04, A61K 31/435
C07F 9/6561, A61K 31/66
C07D 213/74, 333/20
C07C 311/17, C07D 307/14
C07D 207/32, 307/52, 277/64
// (C07D 471/04, 235:00, 221:00)

A1

(11) International Publication Number: **WO 93/16075**

(43) International Publication Date: 19 August 1993 (19.08.93)

(21) International Application Number: PCT/GB93/00273

(22) International Filing Date: 10 February 1993 (10.02.93)

(30) Priority data:
9202791.1 11 February 1992 (11.02.92) GB

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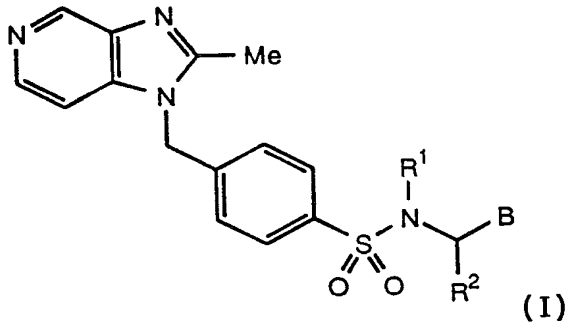
(81) Designated States: AU, CA, FI, JP, KR, NO, NZ, PT, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 4-(1H-2-METHYLIMIDAZO[4,5-c]PYRIDINYLMETHYL)PHENYLSULPHONAMIDE DERIVATIVES AS ANTAGONISTS OF PAF



(I)

(57) Abstract

Compounds of general formula (I); and their pharmaceutically and veterinarily acceptable acid addition salts and hydrates are antagonists of platelet activating factor (PAF) and as such are useful in the treatment or amelioration of various diseases or disorders mediated by PAF.

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4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonamide Derivatives as Antagonists of PAF

This invention relates primarily to novel compounds which are antagonists of platelet activating factor.

Platelet activating factor (PAF) is a bioactive phospholipid which has been identified as 1-*O*-hexadecyl/octadecyl-2-acetyl-*sn*-glyceryl-3-phosphoryl choline. PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a variety of physiological responses which include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, and increased vascular permeability (oedema/erythema). It is known that these physiological effects occur in many inflammatory and allergic diseases and PAF has been found to be involved in a number of such disorders including asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, transplant rejection, gastric ulceration, psoriasis, cerebral, myocardial and renal ischemia. Thus the compounds of the invention, by virtue of their ability to antagonise the actions of PAF, should be of value in the treatment of any of the above conditions and any other conditions in which PAF is implicated (e.g. embryo implantation).

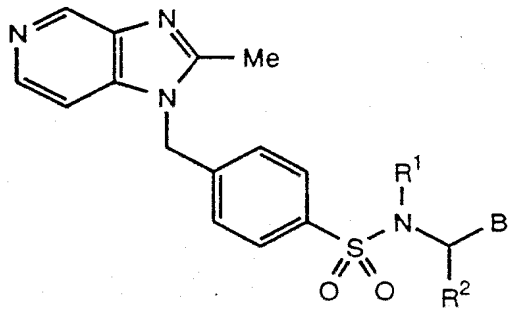
Compounds that have been disclosed as possessing activity as PAF antagonists include compounds which are structurally related to the PAF molecule such as glycerol derivatives (EP-A-0238202), and heterocyclic compounds such as 5-oxy derivatives of tetrahydrofuran (US-4,888,337) and 2,5-diaryl tetrahydrofurans (EP-A-0144804). Recently a more potent 2,5-diaryl tetrahydrofuran derivative, (*trans*)-2-(3-methoxy-5-methylsulphonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (L-659,989) has been disclosed (EP-A-0199324). In our International patent application No. WO 91/17157 we disclose a series of γ-butyrolactol derivatives as PAF antagonists. The compounds of WO 91/17157 differ from the 5-oxy derivatives of tetrahydofuran described in US-4,888,337 and from the 2,5-diaryl tetrahydrofurans such as L-659,989, in that they feature an appended heterocycle with an unsubstituted sp^2 nitrogen atom. There are a number of other PAF antagonists, in addition to those of WO 91/17157, for which the presence of a heterocyclic sp^2 nitrogen atom appears to be an important

requirement for activity (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)).

For the compounds of the present invention the presence of a heterocyclic group possessing an unsubstituted sp^2 nitrogen atom is also a requirement for PAF antagonist activity. However, the compounds of the present invention differ from the other PAF antagonists referred to above in that they are amino acid derivatives.

The present invention provides novel and useful substituted amino acid derivatives and their pharmaceutically acceptable acid addition salts, and pharmaceutical uses thereof as PAF antagonists.

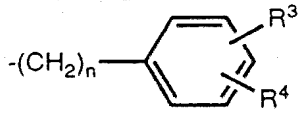
According to a first aspect of the invention there is provided a compound of general formula I;



I

wherein:

R^1 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(COC_1-C_6 alkyl)phenyl, -(CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D represents a group:



wherein n is an integer from 0 to 3, and each of R^3 and R^4 is independently hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, halogen, -CN, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CONH(C_1$-C_6 alkyl)2, -CHO, -CH_2OH, -CF_3, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2 or -NHCOMe;

R^2 represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)2, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

B represents a) a -$(CH_2)_m$X group wherein m is an integer from 0 to 2 and the group X represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen, -C_1-C_4 perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, -$CONH_2$, a group -D wherein D is as defined above, -R^5, -OR^5, -SR^5, -SOR^5, -SO_2R^5, -NHR^5, -NR^5R^5, -CO_2R^5 or -$CONHR^5$ wherein R^5 is -C_1-C_{18} alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl or -C_4-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, -C_1-C_4 perfluoroalkyl, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group;

b) a group Y, wherein Y is -CH_2OH, -$CH_2OC(=O)R^6$, -$CH_2OC(=O)C(=O)OR^6$, -$CH_2OSO_2R^6$, -$CH_2OP(=O)OR^6OR^6$, -NHC(C=O)OR^6, -$CH_2OC(=O)NHR^6$, -$CH_2CO_2R^6$ or -$CH_2OC(=O)CH_2SR^6$ group wherein R^6 is, -C_1-C_{18} alkyl, -C_2-C_{20} alkenyl, -C_2-C_{18} alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, a group D as defined above or a group -$(CH_2)_m$X as defined above;

c) a -$CH_2OC(=O)CHR^2Y$ group wherein R^2 and Y are as defined above;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

Hereafter in this specification the term "compound" includes "salt" or "hydrate" unless the context requires otherwise.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C_1-C_6 alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to six carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

As used herein the term "C_1-C_{18} alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to eighteen carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, decyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, and octadecyl. From one to six carbon atoms may be preferred.

As used herein the term "C_2-C_6 alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_{20} alkenyl" refers to straight chain, branched chain or cycloalkenylalkenyl hydrocarbon groups having from two to twenty carbon atoms and having in addition one or more double bonds, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl, geranyl, retinyl and farnesyl. From two to six carbon atoms may be preferred.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "C_2-C_{18} alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to eighteen carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 10-undecynyl, 4-ethyl-1-octyn-3-yl, 7-dodecynyl, 9-dodecynyl, 10-dodecynyl, 3-methyl-1-dodecyn-3-yl, 2-tridecynyl, 11-tridecynyl, 3-tetradecynyl, 7-hexadecynyl and 3-octadecynyl. From two to six carbon atoms may be preferred.

As used herein, the term "C_1-C_4 perfluoroalkyl" refers to straight chain or branched chain groups having from one to four carbon atoms and substituted by more than one fluorine atom. This term would include for example, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoro-n-propyl, sexafluoro-i-propyl, septafluoro-n-propyl, septafluoro-i-propyl, 4,4,4-trifluoro-n-butyl, nonafluoro-n-butyl, nonafluoro-sec-butyl and nonafluoro-i-butyl.

As used herein the term "OC_1-C_6 alkyl" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

As used herein the term "SC_1-C_6 alkyl" refers to straight chain or branched chain alkylthio groups having from one to six carbon atoms. Illustrative of such alkyl groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio and hexylthio.

As used herein, the term "C_3-C_8 cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "C_4-C_8 cycloalkenyl" refers to an alicyclic group having from 4 to 8 carbon atoms and having in addition one or more double bonds. Illustrative of such cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein, the term "side chain of a naturally occurring amino acid" includes the side chains of alanine, arginine, asparagine, aspartic acid, cysteine,

cystine, glutamic acid, glycine, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α-aminoadipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine, ornithine, pipecolic acid, and thyroxine. The amino acid side chains may be protected; for example the carboxyl groups of aspartic acid, glutamic acid and α-aminoadipic acid may be esterified (for example as a C_1-C_6 alkyl ester), the amino groups of lysine, ornithine, 5-hydroxylysine, 4-hydroxyproline may be converted to amides (for example as a COC_1-C_6 alkyl amide) or carbamates (for example as a $C(=O)OC_1$-C_6 alkyl or $C(=O)OCH_2Ph$ carbamate), the hydroxyl groups of 5-hydroxylysine, 4-hydroxyproline, serine, threonine, tyrosine, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine and thyroxine may be converted to ethers (for example a C_1-C_6 alkyl or a (C_1-C_6 alkyl)phenyl ether) or esters (for example a $C(=O)C_1$-C_6 alkyl ester) and the thiol group of cysteine may be converted to thioethers (for example a C_1-C_6 alkyl thioether) or thioesters (for example a $C(=O)C_1$-C_6 alkyl thioester). The stereochemistry at the carbon atom to which the amino acid side chain is attached may be either D or L.

As used herein, the term "5- or 6-membered heterocyclic ring" refers to such rings having from 5 to 6 atoms in the ring wherein the heteroatom(s) may be one or more nitrogen, oxygen or sulphur atoms. For example heterocycles containing nitrogen, oxygen, or sulphur alone or containing two nitrogen atoms, a nitrogen and an oxygen atom, a nitrogen and a sulphur atom, two nitrogen atoms and an oxygen atom, two nitrogen atoms and a sulphur atom, three nitrogen atoms or four nitrogen atoms.

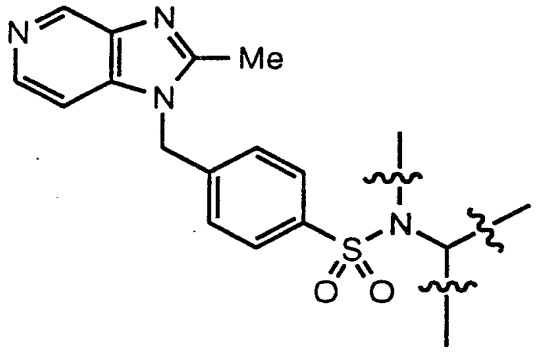
As used herein, the term "heteroaryl" refers to a 5- or 6- membered substituted or unsubstituted aromatic heterocycle containing one or more heteroatoms. Illustrative of such rings are thienyl, furyl, imidazolyl, oxadiazolyl, pyridinyl, pyrazinyl each of which may be optionally substituted by methyl or methoxy.

In compounds of this invention, the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral centre. The invention is understood to include all such diastereoisomers, their optically active enantiomers and mixtures thereof.

The term "pharmaceutically or veterinarily acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human or animal consumption.

Examples of pharmaceutically and/or veterinarily acceptable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate and tartrate salts.

It is considered that the main structural feature of compounds of general formula I that is particularly significant in providing their PAF antagonist activity, is the subunit (i)



(i)

There may be considerable variation of the substituent groups R^1, R^2 and B without loss of such activity. Any of the the wide range of substituents R^1, R^2 and B defined above may be used with retention of PAF antagonist activity. Though a preferred substituent for the group R^2 is the side chain of the amino acid L-leucine (i.e. sec-butyl).

The 1H-2-methylimidazo[4,5-c]pyridinyl group of the subunit is an important requirement for PAF antagonist activity. However, it is expected that PAF antagonist activity may be found in compounds analogous to those of general formula I above, wherein the 1H-2-methylimidazo[4,5-c]pyridinyl group is replaced by a different sp^2 nitrogen heterocycle. The variety of sp^2 nitrogen heterocycles that could provide PAF antagonist activity include those disclosed in our patent application WO 91/17157 and those recently described by Whittaker (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)) and Cooper (Cooper, K., *et al.*, J. Med. Chem. 35(17), 3115-3129 (1992)). The exact nature of the interaction of the sp^2 nitrogen heterocycle and the receptor has not been determined, but it would appear that it is important for the

heterocycle to possess at least one unsubstituted sp^2 nitrogen atom within the heterocyclic ring.

Although in this application the only substituents claimed for the subunit (i) are R^1, R^2 and B it is understood that the introduction of further substituents on the 2-methylimidazo[4,5-c]pyridinyl group, the benzylic carbon atom and/or the 1,4-disubstituted phenyl ring of subunit (i) will lead to compounds that retain PAF antagonist activity.

Preferred compounds include those in which, independently or in any compatible combination:

R^1 represents a hydrogen atom, a $-C_1-C_6$ alkyl (for example methyl, ethyl or propyl) group, a $-C_2-C_6$ alkenyl (for example allyl) group or a group -D;

R^2 represents a hydrogen atom, a $-C_1-C_6$ alkyl (for example ethyl, n-butyl or t-butyl) group, a $-C_2-C_6$ alkenyl (for example allyl) group, a $-(C_1-C_6$ alkyl)C_3-C_8 cycloalkyl (for example cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl) group, a side chain of a naturally occurring amino acid (for example the side chain of leucine, isoleucine, phenylalanine, valine, tryptophan, methionine or tyrosine) or a group D;

in the group D, R^3 represents a hydrogen atom, a $-C_1-C_6$ alkyl (for example methyl) group, a halogen (for example fluorine, chlorine or bromine) atom, a $-CF_3$ group or a $-OC_1-C_6$ alkyl (for example methoxy) group;

in the group D, R^4 represents a hydrogen atom or a $-OC_1-C_6$ alkyl (for example methoxy) group;

in the group $-(CH_2)_mX$, X represents a furanyl (for example furan-2-yl) group, a thienyl (for example thien-2-yl) group, a pyrrolinyl (for example pyrrol-2-yl) group, a tetrahydrofuranyl (for example tetrahydrofuran-2-yl) group, an oxadiazolyl (for example 1,2,4-ozadiazol-5-yl, 1,2,4-ozadiazol-3-yl or 1,3,4-oxadiazol-2-yl) group, a thiadiazolyl (for example 1,2,4-thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl) group, a pyridinyl (for example pyridin-2-yl, pyridin-3-yl or pyridin-4-yl) group, a piperazinyl (for example piperazin-1-yl) group, a benzotriazolyl (for example benzotriazol-2-yl) group, a pyrazinyl (for example pyrazin-2-yl) group, a pyridazinyl (for example 1,2-pyridazin-3-yl) group, a

pyrimidinyl (for example 1,3-pyrimidin-5-yl) group, a dithianyl (for example 1,3-dithian-2-yl) group, a benzo[b]thienyl (for example benzo[b]thien-2-yl) group, a isoxazolyl (for example isoxazol-5-yl) group or a quinolinyl (for example quinolin-3-yl);

the group X may be optionally substituted with one or more substituents selected from hydrogen, a group -D, -R^5 or -CO_2R^5.

R^5 represents a -C_1-C_{18} alkyl (for example methyl, ethyl, n-propyl, n-butyl or heptadecyl) group or a -OC_1-C_6 alkyl (for example methoxy) group;

R^6 represents a -C_1-C_{18} alkyl (for example methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl or n-octadecyl) group, a -C_2-C_{20} alkenyl (for example retinyl) group, a group -D or a group -$(CH_2)_m$X;

Exemplary compounds include:

1. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
2. N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
3. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-D-leucinol,
4. N-Ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
5. N-Allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
6. N-Propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
7. N-Benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
8. N-4-Methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
9. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-isoleucinol,

10. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylalaninol,
11. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-valinol,
12. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-tryptophanol,
13. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-methioninol,
14. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-O-methyl-L-tyrosinol,
15. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-norleucinol,
16. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylglycinol,
17. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylglycinol,
18. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-ethylglycinol,
19. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-allylglycinol,
20. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopropylalaninol,
21. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopentylalaninol,
22. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclohexylalaninol,
23. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
24. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-D-leucinol,
25. O-Ethanoyl-N-ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
26. O-Ethanoyl-N-allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
27. O-Ethanoyl-N-propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
28. O-Ethanoyl-N-benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,

29. O-Ethanoyl-N-4-methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
30. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-isoleucinol,
31. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-phenylalininol,
32. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-valinol,
33. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-tryptophanol,
34. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-methioninol,
35. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-O'-methyl-L-tyrosinol,
36. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-norleucinol,
37. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-phenylglycinol,
38. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-t-butylglycinol,
39. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-D,L-ethylglycinol,
40. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-D,L-allylglycinol,
41. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclopropylalininol,
42. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclopentylalininol,
43. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclohexylalininol,
44. O-Octadecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
45. O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
46. O-2-Furoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
47. O-Ethyloxaloyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,

48. O-Benzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
49. O-2-Acetoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
50. O-Propanoyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
51. O-Propanoyl-N-ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
52. O-Propanoyl-N-allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
53. O-Propanoyl-N-methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
54. O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-isoleucinol,
55. O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclopentylalininol,
56. O-Butanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
57. O-Pentanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
58. O-Hexanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
59. O-Octanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
60. O-Decanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
61. O-Dodecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
62. O-Tetradecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
63. O-Hexadecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
64. O-2-Thiophenecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
65. O-2-Tetrahydrofuroyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
66. O-2-Pyridinecarbonyl-N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,

67. O-3-Pyridinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
68. O-4-Pyridinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
69. O-3-Quinolinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
70. O-2-Trifluoromethylbenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
71. O-2-Bromobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
72. O-3-Chlorobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
73. O-4-Methoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
74. O-4-Fluorobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
75. O-3,4-Dimethoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
76. O-3-Chloro-4-methoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
77. O-2,2-Dimethylpropanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
78. O-2-(3,4-Dimethoxyphenylmercapto)ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
79. O-Retinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
80. O-2-(4-Methoxyphenyl)ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
81. O-2-(3,4-Dimethoxyphenyl)ethanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
82. O-3-(4-Methoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
83. O-3-(3,4-Dimethoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
84. O-3-(3-Chloro-4-methoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
85. O-3-(Pyridin-3-yl)propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,

86. O-(N'-Benzyloxycarbonyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
87. O-(N',N'-Dibenzyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
88. O-(N'-Benzyloxycarbonyl)glycinoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
89. O-(N'-Benzyloxycarbonyl)-D-leucinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
90. O-(N'-Benzyloxycarbonyl)-L-phenylalininoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
91. O-(N',N'-dibenzyl)glycinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
92. O-(N'-Benzyloxycarbonyl)-L-norleucinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
93. O-(N'-Butoxycarbonyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
94. O-(N'-Benzyloxycarbonyl)-L-valinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
95. O-(N'-Benzyloxycarbonyl)-L-phenylglycinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
96. O-Diethoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
97. O-Dimethoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
98. O-Diphenoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
99. O-Diisopropoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
100. O-Methylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
101. O-Ethylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
102. O-Propylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
103. O-Phenylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
104. O-4-Methylphenylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,

105. O-Benzylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
106. O-4-Ethoxycarbonylpiperazinecarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
107. O-5-Ethyl-1,3,4-thiadiazol-2-ylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
108. O-Pyridin-2-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
109. O-Octadecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
110. O-Methylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
111. O-Ethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
112. O-n-Propylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
113. O-i-Propylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
114. O-n-Pentylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
115. O-n-Hexylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
116. O-n-Octylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
117. O-n-Decylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
118. O-n-Dodecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
119. O-n-Tetradecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
120. O-n-Hexadecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
121. O-t-Butylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
122. O-Pyridin-2-ylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
123. O-Pyridin-4-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,

124. O-Pyridin-3-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
125. O-4-Methoxyphenylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
126. O-3,4-Dimethoxybenzylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
127. O-2-(4-Methoxyphenyl)ethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
128. O-2-(3,4-Dimethoxyphenyl)ethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
129. O-3-(3,4-Dimethoxyphenyl)propylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
130. O-3-(Pyridin-3-yl)propylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
131. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-2-thienylmethylamine,
132. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyltetrahydrofurfurylamine,
133. N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-(N'-methylpyrrol-2-yl)ethylamine,
134. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(4-fluorophenyl)-1-(2-thienyl)methylamine,
135. N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)propylamine,
136. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(2-furyl)-3-methylbutylamine,
137. N-4-(1H-2-Methylbenzimidazolylmethyl)phenylsulphonyl-1-(2-benzothiazolyl)-3-methylbutylamine,
138. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(2-thienyl)-3-methylbutylamine,
139. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(pyridin-3-yl)-3-methylbutylamine,
140. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(N'-methyl-2-pyrrolyl)-3-methylbutylamine,
141. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(pyrazin-2-yl)-3-methylbutylamine,
142. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(6-methylpyrazin-2-yl)-3-methylbutylamine,

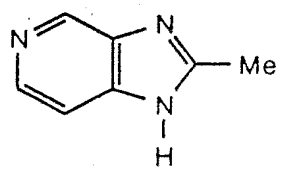
143. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-ethylpyrazin-2-yl)-3-methylbutylamine,
144. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-ethyl-1,2-pyridazin-3-yl)-3-methylbutylamine,
145. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-ethyl-1,3-pyrimidin-5-yl)-3-methylbutylamine
146. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(1,3-dithian-2-yl)-3-methylbutylamine,
147. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)pentylamine,
148. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(4-fluorophenyl)-1-(2-furyl)methylamine,
149. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-(4-methoxyphenyl)-1-(2-furyl)ethylamine,
150. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-2-yl)-3-methylbutylamine,
151. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-methoxypyridin-3-yl)-3-methylbutylamine,
152. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-3-ylmethyl)-3-methylbutylamine,
153. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-benzo[b]thienyl)-3-methylbutylamine,
154. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-methylisoxazol-5-ylmethyl)-3-methylbutylamine,
155. N-Methyl-N-4-(1H-2-methylbenzimidazolylmethyl)phenylsulphonyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
156. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
157. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-heptadecyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
158. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-propyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
159. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-n-butyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
160. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
161. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-benzyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,

162. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
163. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-ethyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
164. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-propyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
165. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
166. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-β-alanine ethyl ester,
167. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid ethyl ester,
168. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid isopropyl ester,
169. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid n-butyl ester,
170. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid benzyl ester,
171. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-4-phenylbutanoic acid ethyl ester,
172. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-4-(4-methoxyphenyl)butanoic acid ethyl ester.

Compounds of general formula I may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

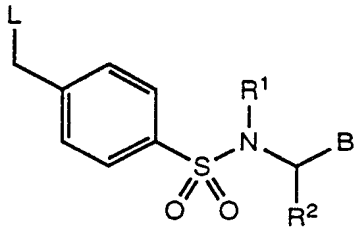
According to a second aspect of the invention, there is provided a process for preparing a compound of general formula I as defined above, the process comprising:

(a) treating an imidazole derivative represented by general formula II



II

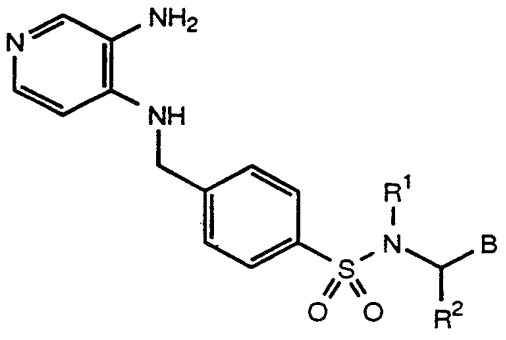
with a suitable base (e.g. sodium hydride, potassium hydride, sodium bis(trimethylsilyl)amide, or potassium hydroxide), followed by a compound of general formula III



III

wherein R^1, R^2 and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

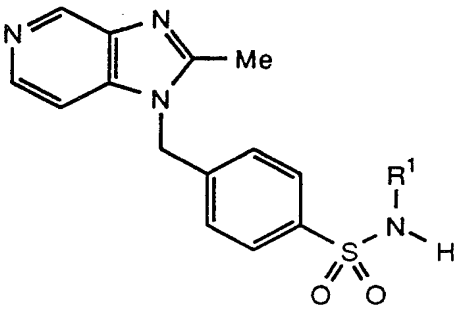
(b) treating a substituted diamino compound of general formula IV



IV

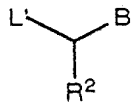
wherein R^1, R^2 and B are as defined in general formula I, with acetic acid or a suitable derivative thereof; or

(c) treating a sulphonamide of general formula V



V

wherein R^1 is as defined in general formula I, with a compound of general formula VI



VI

wherein R^2 and B are as defined in general formula I and L' is hydroxyl, chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; and

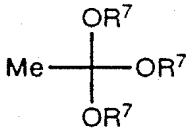
(d) optionally after step (a), step (b) or step (c) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

The reaction of step (a) can for preference be conducted in an aprotic solvent (e.g. tetrahydrofuran, N,N-dimethylformamide or acetonitrile) to yield compounds of general formula I. In the case where an unsymmetrically substituted imidazole derivative is used the reaction can yield an isomeric mixture, which is separated by chromatography to yield compounds of general formula I.

In step (b), derivatives of acetic acid, which are suitable substrates for the reaction include acetyl halides of general formula VII

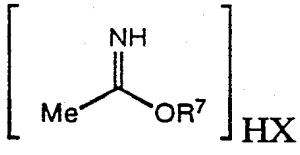
$$MeCO_2X \qquad \text{VII}$$

wherein X is fluoride, chloride, bromide or iodide; trialkylorthoesters of general formula VIII



VIII

wherein R^7 is -C_1-C_6 alkyl; imino ether salts of general formula IX



IX

wherein R^7 and X are as defined above, or acetic anhydride. Acetyl halides of general formula VII, trialkylorthoesters of general formula VIII and imino ether salts of general formula IX are available in the art or can be prepared by methods analogous to those known in the art

The reaction of step (c) can be conducted in the presence of triphenylphosphine and diethyl azodicarboxylate in an aprotic solvent (e.g. tetrahydrofuran) when L' is hydroxyl and in the presence of a base (e.g. sodium hydride, potassium hydride, sodium bis(trimethylsilyl)amide, or potassium hydroxide) in an aprotic solvent (e.g. tetrahydrofuran) when L' is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy.

By means of step (d) certain compounds of general formula I wherein B is as defined in general formula I but is not a $-CH_2OC(=O)NHR^6$ or $-NHC(C=O)OR^6$ group, may be prepared by treatment of a compound of general formula I wherein R^2 is hydrogen with base followed by an electrophile of general formula X

$$LR^2 \qquad X$$

wherein R^2 is as defined in general formula I but is not a hydrogen atom, a phenyl or a substituted phenyl group, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy. Electrophiles of general formula X are available in the art or can be prepared by procedures known to those skilled in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a $-CH_2OC(=O)R^6$ group may be prepared by treatment of a compound of general formula I wherein B is a $-CH_2OH$ group with a suitable carboxylic acid derivative of general formula XI

$$R^6C(=O)Q \qquad XI$$

wherein R^6 is as defined in general formula I and Q is a hydrogen atom, halide or a $-(O=)CR^6$ group. The conditions for this reaction will depend on the nature of the group Q and will be apparent to one skilled in the art. The reaction will usually be carried out in the presence of a suitable base (e.g. triethylamine,

pyridine and/or 4-dimethylaminopyridine) in an aprotic solvent (e.g. tetrahydrofuran or dichloromethane). Carboxylic acid derivatives of the general formula XI are available in the art or can be prepared by methods analogous to those known in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a $-CH_2OSO_2R^6$ group may be prepared by treatment of a compound of general formula I wherein B is a $-CH_2OH$ group with a suitable sulphonyl halide of general formula XII

$$R^6SO_2Hal \qquad XII$$

wherein R^6 is as defined in general formula I and Hal is fluoro, chloro, bromo or iodo, in the presence of a suitable base (e.g. triethylamine) in an aprotic solvent (e.g. tetrahydrofuran or dichloromethane). Sulphonyl halides of general formula XII are available in the art or can be prepared by methods analogous to those known in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a $-CH_2OP(=O)OR^6OR^6$ group may be prepared by treatment of a compound of general formula I wherein B is a $-CH_2OH$ group with a suitable halophosphate of general formula XIII

$$R^6OR^6OP(=O)Hal \qquad XIII$$

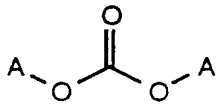
wherein R^6 is as defined in general formula I and Hal is fluoro, chloro, bromo or iodo, in the presence of a suitable base (e.g. triethylamine) in an aprotic solvent (e.g. tetrahydrofuran or dichloromethane). Halophosphates of general formula XIII are available in the art or can be prepared by methods analogous to those known in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a $-CH_2OC(=O)NHR^6$ group may be prepared by treatment of a compound of general formula I wherein B is a $-CH_2OH$ group with an isocyanate of general formula XIV

$$R^6\text{-}N=C=O \qquad XIV$$

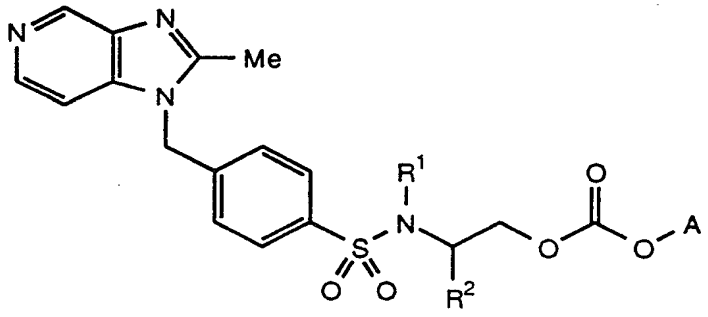
wherein R^6 is as defined in general formula I. Isocyanates of general formula XIV are available in the art or can be prepared by methods analogous to those known in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a $-CH_2OC(=O)NHR^6$ group may be prepared by a two step process involving initial treatment of a compound of general formula I wherein B is a $-CH_2OH$ group with a reagent of general formula XV



XV

wherein A is a pyridin-2-yl or N-succinimidyl group, in the presence of a suitable base (e.g. triethylamine) in an aprotic solvent (e.g. dichloromethane) to give an anhydride of general formula XVI



XVI

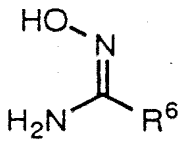
wherein R^1 and R^2 are as defined in general formula I and A is as defined above, and subsequent treatment of the anhydride of general formula XVI with an amine of general formula XVII

$$R^6NH_2 \qquad \text{XVII}$$

wherein R^6 is as defined in general formula I. Each step is for preference conducted in an aprotic solvent (e.g. dichloromethane). Reagents of general formula XV are available in the art or can be prepared by methods analogous to those known in the art. Amines of general formula XVII are available in the art or can be prepared by methods analogous to those known in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a $-CH_2OH$ group may be prepared by the reduction of a compound of general formula I wherein B is a $-CH_2OC(=O)R^6$ or $-CO_2R^6$ group with a suitable hydride reducing reagent (e.g. lithium aluminium hydride or diisobutylaluminium hydride) in an aprotic solvent (e.g. tetrahydrofuran or toluene).

Also by means of step (d) certain compounds of general formula I wherein B is a 1,2,4-oxadiazol-5-yl group may be prepared by treatment of a compound of general formula I wherein B is a $-CO_2H$ group with pentafluorophenol and a coupling agent such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide in a solvent such as dichloromethane. The resulting pentafluorophenyl ester is treated with an amide oxime of general formula XVIII



XVIII

wherein R^6 is as defined in general formula I in a suitable aprotic solvent (e.g. chloroform), followed by cyclisation under Dean-Stark conditions in suitable solvent (e.g. xylene, toluene, benzene or ethyl acetate). The cyclisation may be aided by the addition of activated molecular sieves. Amide oximes of general formula XVIII are known in the art or may be prepared by methods analogous to those known in the art.

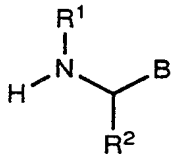
Also by means of step (d) certain compounds of general formula I wherein B is a 1,2,4-oxadiazol-5-yl group may be prepared by treatment of a compound of general formula I wherein B is a $-CO_2NH_2$ group, with a derivative $R^5C(OR^8)_2N(R^9)_2$ wherein R^5 is as defined in general formula I and R^8 and R^9 are independently $-C_1$-C_6 alkyl followed by hydroxylamine under dehydrating conditions such as heating in acetic acid with a co-solvent (e.g. dioxane). Compounds of general formula I wherein B is a $-CO_2NH_2$ group may be obtained by treatment of a compound of general formula I wherein B is a $-CO_2R^6$, wherein R^6 is as defined in general formula I, with ammonia. Derivatives $R^5C(OR^8)_2N(R^9)_2$ are known in the art or may be prepared by methods analogous to those known in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a 1,2,4-oxadiazol-3-yl group may be prepared by treatment of a compound of general formula I wherein B is a -CN group with hydroxylamine followed by heating with a carboxylic acid derivative of general formula $R^5C(=O)Q$, $R^5C(=NH)R^7$ or $R^5C(-OR^7)_3$ wherein R^5 is as defined in general formula I, Q is a halide, 4-nitrophenoxy or $-(O=)CR^5$ group, and R^7 is as defined above. Compounds of general formula I wherein B is a -CN group may be obtained by dehydration of a compound of general formula I wherein B is a $-CO_2NH_2$. Carboxylic acid derivatives of general formula $R^5C(=O)Q$, $R^5C(=NH)R^7$ or $R^5C(OR^7)_3$ are known in the art or may be prepared by methods analogous to those known in the art.

Also by means of step (d) certain compounds of general formula I wherein B is a 1,3,4-oxadiazol-2-yl group may be prepared by treatment of a compound of general formula I wherein B is a $-CO_2Q$ group, wherein Q is a halide, 4-nitrophenoxy, pentafluorophenoxy, $-OC_1$-C_6 alkyl or $-(O=)CC_1$-C_6 alkyl group, with hydrazine followed by a carboxylic acid derivative of general formula $R^5C(=O)Q$, $R^5C(=NH)R^7$ or $R^5C(OR^7)_3$, wherein R^5 is as defined in general formula I, Q is a halide, 4-nitrophenoxy, pentafluorophenoxy or $-(O=)CR^5$ group, and R^7 is as defined above, with heating.

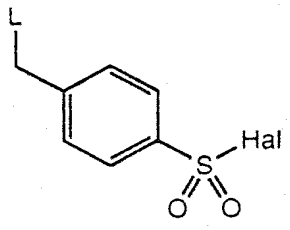
Imidazole derivatives of general formula II are available in the art or can be prepared by methods analogous to those known in the art.

Compounds of general formula III may be prepared by treatment of an amine of general formula XIX



XIX

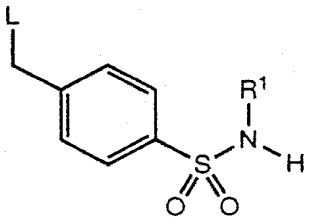
wherein R^1, R^2 and B are as defined in general formula I, with a sulphonyl halide of general formula XX



XX

wherein L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy and Hal is a halide (e.g. fluoro, chloro or bromo), in the presence of a suitable base (e.g. triethylamine) in a suitable aprotic solvent (e.g. dichloromethane, tetrahydrofuran, ethyl acetate or dioxan). Amines of general formula XIX and sulphonyl halides of general formula XX are known in the art or may be prepared by methods known in the art.

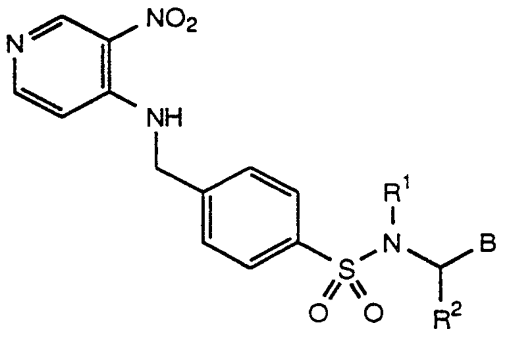
Alternatively compounds of general formula III may be prepared by the treatment of a sulphonamide of general formula XXI



XXI

wherein R^1 is as defined in general formula I, with a compound of general formula VI in the presence of triphenylphosphine and diethyl azodicarboxylate in an aprotic solvent (e.g. tetrahydrofuran) when L' is hydroxyl and in the presence of a base (e.g. sodium hydride, potassium hydride, sodium bis(trimethylsilyl)amide, or potassium hydroxide) in an aprotic solvent (e.g. tetrahydrofuran) when L' is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy. Sulphonamides of general formula XXI and alcohols of general formula VI are known in the art or may be prepared by methods known in the art.

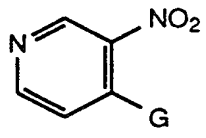
Substituted 1,2-diamines of general formula IV may be prepared by the reduction of a substituted 1,2-nitroamine of general formula XXII



XXII

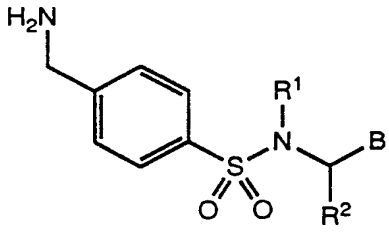
wherein R^1, R^2 and B are as defined in general formula I, for example in the presence of hydrogen and a catalyst such as palladium or platinum.

Substituted 1,2-nitroamines of general formula XXII may be prepared by a number of methods. The first of these methods involves the treatment of a nitro compound of general formula XXIII



XXIII

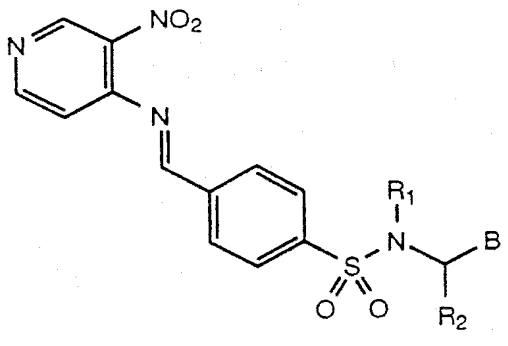
wherein G is halo or $-OC_1-C_6$ alkyl, is treated with an amino compound of general formula XXIV



XXIV

wherein R^1, R^2 and B are as defined in general formula I. Nitro compounds of general formula XXIII are available in the art or can be prepared by methods analogous to those known in the art. Amino compounds of general formula XXIV can be prepared by treatment of a compound of general formula III with hexamethylenetetramine followed by treatment with ethanolic hydrochloric acid or by sequential treatment of a compound of general formula III with sodium azide followed by either triphenylphosphine in 'wet' tetrahydrofuran or hydrogenation over a suitable catalyst.

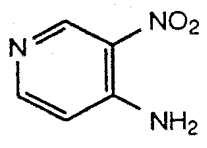
A second procedure for the preparation of substituted 1,2-nitroamines of general formula XXII involves the reduction of an imino nitro compound of general formula XXV



XXV

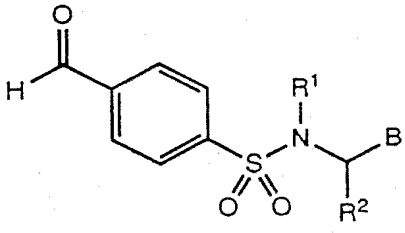
wherein R^1, R^2 and B are as defined in general formula I, for example by the action of sodium cyanoborohydride.

The imino nitro compounds of general formula XXV may be prepared by treating a 1,2-nitroamine of formula XXVI



XXVI

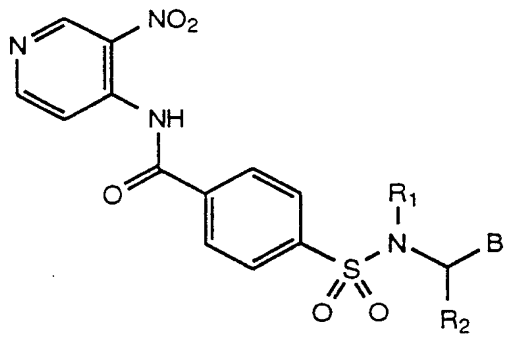
with a substituted carbonyl derivative of general formula XXVII



XXVII

wherein R^1, R^2 and B are as defined in general formula I. The 1,2-nitroamine of formula XXVI is available in the art or can be prepared by methods analogous to those known in the art. Substituted carbonyl derivatives of general formula XXVII may be prepared by treatment of a compound of general formula III with an oxidising agent (e.g. dimethyl sulphoxide), or by treatment of a compound of general formula III with hexamethylenetetramine in aqueous ethanol.

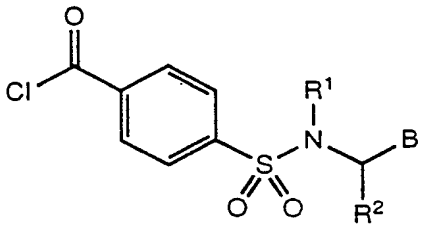
Alternatively substituted 1,2-nitroamines of general formula XXII may be prepared by the reduction of a 1,2-nitroamide of general formula XXVIII



XXVIII

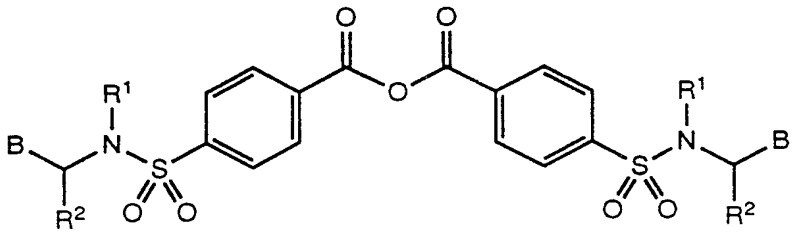
wherein R^1, R^2 and B are as defined in general formula I, with a suitable metal hydride reducing agent such as for example lithium aluminium hydride.

The 1,2-nitroamides of general formula XXVIII may be prepared by the coupling of a 1,2-nitroamine of formula XXVI with an acid chloride of general formula XXIX



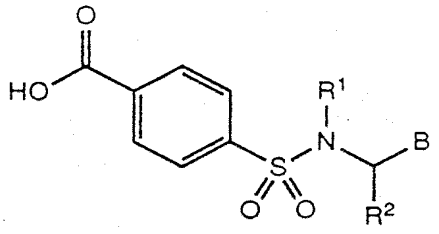
XXIX

wherein R^1, R^2 and B are as defined in general formula I, in an aprotic solvent and in the presence of a suitable base such as, for example, triethylamine. Alternatively, the reaction may be conducted utilising an acid anhydride of general formula XXX



XXX

wherein R^1, R^2 and B are as defined in general formula I. Another procedure for preparing 1,2-nitroamides of general formula XXVII involves reaction of a 1,2-nitroamine of formula XXVI with a carboxylic acid of general formula XXXI



XXXI

wherein R^1, R^2 and B are as defined in general formula I, in the presence of a coupling reagent (e.g. 1,3-dicyclohexylcarbodiimide). Acid chlorides of general formula XXIX, acid anhydrides of general formula XXX and carboxylic acids of general formula XXXI may be prepared from carbonyl derivatives of general formula XXVII by procedures known to those skilled in the art.

Sulphonamides of general formula V may be prepared by methods analogous to those described in steps (a) and (b) above for the preparation of compounds of general formula I.

The appropriate solvents employed in the above reactions are solvents wherein the reactants are soluble but do not react with the reactants. The preferred solvents vary from reaction to reaction and are readily ascertained by one of ordinary skill in the art.

Compounds of general formulae III, IV and V are valuable intermediates in the preparation of compounds of general formula I, as are other novel compounds specifically or generically disclosed herein. According to a third aspect of the invention, there is therefore provided a compound of general formula III. According to a fourth aspect of the invention, there is provided a compound of general formula IV. According to a fifth aspect of the invention, there is provided a compound of general formula V.

This invention also relates to a method of treatment for patients (or animals including mammalian animals raised in the dairy, meat, or fur trades or as pets) suffering from disorders or diseases which can be attributed to PAF as previously described, and more specifically, a method of treatment involving the

administration of PAF antagonists of general formula I as the active ingredient. In addition to the treatment of warm blooded animals such as mice, rats, horses, cattle, pigs, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

According to a sixth aspect of the invention there is provided a compound of general formula I for use in human or veterinary medicine particularly in the management of diseases mediated by PAF; compounds of general formula I can be used among other things to reduce inflammation and pain, to correct respiratory, cardiovascular, and intravascular alterations or disorders, and to regulate the activation or coagulation of platelets, to correct hypotension during shock, the pathogenesis of immune complex deposition and smooth muscle contractions.

According to an seventh aspect of the invention there is provided the use of a compound of general formula I in the preparation of an agent for the treatment or prophylaxis of PAF-mediated diseases and/or the treatment of inflammatory disorders; such as rheumatoid arthritis, osteoarthritis and eye inflammation, cardiovascular disorder, thrombocytopenia, asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, cerebral, myocardial and renal ischemia and any other condition in which PAF is implicated.

Compounds of general formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

According to a eighth aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula I and a pharmaceutically and/or veterinarily acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be

in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene

oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may

also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical application to the skin compounds of general formula I may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, compounds of general formula I may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hypromellose may also be included.

Compounds of general formula I may be administered parenterally in a sterile medium. The drug depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of general formula I may be used for the treatment of the respiratory tract by nasal or buccal administration of, for example, aerosols or sprays which can disperse the pharmacological active ingredient in the form of a

powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 1.0 mg to about 3.5 g per patient per day). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

It has been found that the compounds of general formula I exhibit *in vitro* and *in vivo* antagonistic activities with respect to PAF. Compounds of general formula

I inhibit PAF-induced functions in both the cellular and tissue levels by changing the PAF binding to its specific receptor site. The ability of compounds of general formula I to inhibit the binding of PAF to its specific receptor binding site on human platelet plasma membranes was measured according to Pharmacological Example 1. The ability of compounds of general formula I to reverse the hypotension caused by an infusion of PAF in rats was measured according to Pharmacology Example 2.

The following examples illustrate the invention, but are not intended to limit the scope in any way.

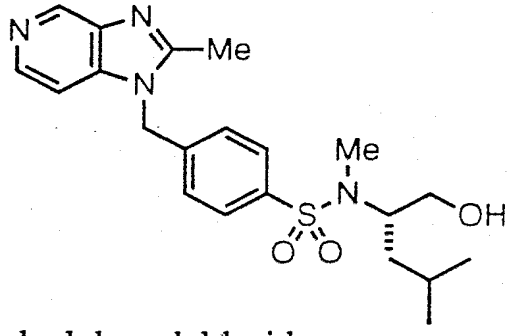
The following abbreviations have been used in the Examples:-

DCM - Dichloromethane
DIPE - Diisopropylether
DMF - N,N-Dimethylformamide
HPLC - High performance liquid chromatography
NBS - N-Bromosuccinimide
TDA-1 - Tris(2-(2-methoxyethoxy)ethyl)amine
THF - Tetrahydrofuran
TLC - Thin layer chromatography

Column chromatography was performed with "flash" grade silica gel. Unless otherwise stated anhydrous magnesium sulphate or anhydrous sodium sulphate was used for drying organic solutions. Unless otherwise stated ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 MHz and 62.9 MHz respectively using $CDCl_3$ as a solvent and internal reference and are reported as δ ppm from TMS.

Example 1

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol



(a) 4-Bromomethylphenylsulphonylchloride

To a solution of p-toluenesulphonyl chloride (50 g, 0.26 mol) in benzene (150 ml) and NBS (46.7 g, 0.26 mol) heated at reflux was added 2,2'-azobis(2-methylpropionitrile) (100 mg). The mixture was heated at reflux for 12 h and allowed to cool to room temperature. The white precipitate of succinimide that formed was separated and discarded. The filtrate was taken up in DCM (200 ml) and washed with water (3 x 100 ml) followed by brine (100 ml) and dried. Filtration, concentration and subsequent crystallisation (from DIPE) gave in two crops 4-bromomethylphenylsulphonylchloride (46.3 g, 66%) as a white crystalline solid.

m.p. 75-76°C

δ_H 8.02 (2H, d, J 8.5 Hz), 7.64 (2H, d, J 8.5 Hz), 4.52 (2H, s).

(b) N-4-Bromomethylphenylsulphonyl-L-leucine ethyl ester

L-leucine ethyl ester hydrochloride (75.0 g. 0.403 mol) was suspended in THF (300 ml) at 0°C, and triethylamine (67 ml, 0.484 mol) added slowly. After stirring for 15 mins a solution of 4-bromomethylphenylsulphonyl chloride (108.4 g, 0.403 mol) in THF (100 ml) was added *via* cannular. The reaction mixture was allowed to stir overnight at ambient temperature. The solvent was removed under low pressure and the organics were extracted into ethyl acetate (200 ml) and washed with water (100 ml) and brine (100 ml). The organic portion was dried, filtered and the solvent evaporated under low pressure. The product was recrystallised from DIPE (500 ml) to give N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester (134.0 g, 85%) as a white crystalline solid.

δ_H 7.84 (2H, d, J 8.3 Hz), 7.52 (2H, d, J 8.3 Hz), 5.06 (1H, d, J 10.1 Hz), 4.61 (2H, s), 3.97-3.82 (3H, m), 1.85-1.79 (1H, m), 1.49 (2H, t, J 7.1 Hz), 1.08 (3H, t, J 7.1 Hz), 0.92 (3H, d, J 6.7 Hz), 0.91 (3H, d, J 6.5 Hz).

(c) N-4-Azidomethylphenylsulphonyl-L-leucine ethyl ester

A solution of sodium azide (75.0 g, 1.054 mol) in water (150 ml) was added to a solution of the N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester (89.0 g, 0.221 mol) in dichloromethane (150 ml). Benzyltriethylammonium chloride (10 g, 0.044 mol) was added and the heterogenous reaction mixture stirred vigorously for 60 h. The organic portion was separated, washed thoroughly

with water, dried, filtered and concentrated to a golden oil, which crystallised on standing. The resulting white solid was freeze dried overnight to yield N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (78.2 g, 97%).

m.p. 75-77°C

Analysis calculated for $C_{15}H_{22}N_4O_4S$
Requires C 50.83 H 6.26 N 15.81
Found C 50.80 H 6.28 N 15.82

i.r. (DCM) 2930, 2100, 1730, 1335, 1150 cm^{-1}

$[\alpha]_D^{25}$ -16.4 (c 2.0, DCM)

δ_H 7.86 (2H, d, J 8.4 Hz), 7.45 (2H, d, J 8.6 Hz), 5.13, (1H, d, J 10.0 Hz), 4.43 (2H, s), 3.98-3.84 (3H, m), 1.83-1.75 (1H, m), 1.49 (2H, dd, J 7.7, 6.7 Hz), 1.09 (3H, t, J 7.1 Hz), 0.91 (3H, d, J 6.7 Hz), 0.89 (3H, d, J 6.5 Hz).

(d) N-Methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester

A 60% dispersion of sodium hydride in mineral oil (9.68 g, 0.242 mol) was added in portions to a solution of N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (78.0 g, 0.220 mol) in THF (200 ml) at 0°C. After stirring for 20 mins iodomethane (28 ml, 0.44 mol) was added slowly, and the reaction allowed to warm to ambient temperature overnight. Saturated ammonium chloride solution (ca. 15 ml) was added and the THF removed under reduced pressure. The resulting residue was taken up in dichloromethane, washed with saturated hydrogen carbonate solution then water, dried, filtered and concentrated to give N-methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester as an orange oil (76.0 g, 94%).

Analysis calculated for $C_{16}H_{24}N_4O_4S$
Requires C 52.16 H 6.57 N 15.21
Found C 52.20 H 6.54 N 15.12

i.r. (DCM) 2100, 1735, 1340, 1160 cm^{-1}

$[\alpha]_D^{20}$ -15.3 (c 2.2, DCM)

δ_H 7.83 (2H, dd, J 8.2, 1.6 Hz), 7.45 (2H, br d, J 8.3 Hz), 4.71-4.65 (1H, m), 4.44 (2H, s), 3.96-3.86 (2H, m), 2.86 (3H, s), 1.67-1.58 (3H, m), 1.09 (3H, t, J 7.1 Hz), 0.99 (3H, d, J 5.0 Hz), 0.97 (3H, d, J 6.1 Hz).

(e) N-Methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester

Triphenylphosphine (101.80 g, 0.388 mol) was added to a solution of N-methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (71.5 g, 0.194 mol) in a mixture of THF and water (4:1, 200 ml), and the reaction mixture stirred overnight at ambient temperature. The THF was removed under reduced pressure, and the product extracted with ethyl acetate, dried, filtered and concentrated to an orange oil. This was purified by chromatography (silica: gradient elution; 1:2 ethyl acetate/hexane; ethyl acetate; 10% methanol in ethyl acetate) to give N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester (38 g, 58%) as a yellow oil.

δ_H 7.76 (2H, dd, J 8.5, 1.7 Hz), 7.45 (2H, d, J 8.3 Hz), 4.71-4.65 (1H, m), 3.95 (2H, s), 3.95-3.85 (2H, m), 2.83 (3H, s), 1.95 (2H, br s), 1.68-1.57 (3H, m), 1.06 (3H, t, J 7.1 Hz), 0.97 (3H, d, J 5.4 Hz), 0.95 (3H, d, J 5.9 Hz).

(f) N-Methyl-N-4-(N'-3-nitropyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester

4-Chloro-3-nitropyridine (6.0 g, 38 mmol) was added to a stirred solution of N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester (13.0 g, 38 mmol) and triethylamine (5.3 ml, 38 mmol) in chloroform (150 ml) at ambient temperature. The reaction mixture was stirred for 60 h, then washed with water, dried, filtered and the solvent removed under reduced pressure to leave a brown oil. This was purified by chromatography over silica (gradient elution; 33% ethyl acetate in hexane; ethyl acetate) to give N-methyl-N-4-(N'-3-nitropyridin-4-yl)aminomethyl-phenylsulphonyl-L-leucine ethyl ester (10.9 g, 62%) as a yellow amorphous solid.

m.p. 71-75°C

i.r. (DCM) 3390, 1730, 1510, 1330 cm^{-1}

$[\alpha]_D^{25}$ -13.8 (c 2.0, DCM)

δ_H 9.00 (1H, s) 8.55 (1H, t, J 5.9 Hz), 8.04 (1H, d, J 6.1 Hz), 7.60 (2H, d, J 8.3 Hz), 7.32 (2H, d, J 8.3 Hz), 6.50 (1H, d, J 6.2 Hz), 4.57 (2H, d, J 5.9 Hz), 4.50-4.44 (1H, m), 3.75-3.62 (2H, m), 2.69 (3H, s), 1.45 (3H, br d), 0.86 (3H, t, J 7.1 Hz) 0.77 (6H, d, J 5.9 Hz).

(g) N-Methyl-N-4-(N'-3-aminopyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester

A solution of N-methyl-N-4-(N'-3-nitropyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester (10.9 g, 0.023 mol) in ethanol (40 ml) was hydrogenated at 100 p.s.i. overnight in the presence of 10% palladium on charcoal (1.0 g). The catalyst was removed by filtration through GF/F filter paper, and the filtrate evaporated under reduced pressure to give N-methyl-N-4-(N'-3-aminopyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester (8.90 g, 87%) as a brown foam.

δ_H 7.86 (1H, s) 7.83 (1H, d, J 5.5 Hz), 7.73 (2H, d, J 8.3 Hz), 7.41 (2H, d, J 8.3 Hz), 6.29 (1H, d, J 5.4 Hz), 5.09-4.97 (1H, m), 4.67-4.61 (1H, m), 4.44 (2H, d, J 5.6 Hz), 3.90-3.81 (2H, m), 2.84 (3H, s), 1.62-1.57 (5H, m), 1.04 (3H, t, J 7.1 Hz), 0.96 (3H, d, J 6.0 Hz), 0.95 (3H, d, J 6.1 Hz).

(h) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester

N-Methyl-N-4-(N'-3-aminopyridin-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester (8.90 g, 20.5 mmol) was refluxed overnight in acetic anhydride (90 ml). The reaction mixture was allowed to cool, then methanol added cautiously until effervescence ceased. The volatiles were removed under reduced pressure and the residue partitioned between saturated sodium hydrogen carbonate solution and ethyl acetate. The organic portion was washed with saturated sodium hydrogen carbonate (x3), and water, dried, filtered and concentrated to a brown oil. This was passed down a pad of silica (3% methanol in DCM) to remove baseline material, and the product further purified by medium pressure liquid chromatography (silica gel: 3% methanol in DCM plus trace of triethylamine) to give a pale yellow oil (5.12 g, 55%), which solidified slowly on standing. Recrystallisation from ethyl acetate/DIPE gave N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester as a white crystalline solid.

m.p. 105°C

Analysis calculated for $C_{23}H_{30}N_4O_4S$
Requires C 60.24 H 6.60 N 12.22
Found C 60.21 H 6.59 N 12.08

i.r. (KBr) 2960, 1730, 1330, 1150 cm^{-1}

$[\alpha]_D^{20}$ -6.7 (c 2.0, CDCl3)

δ_H 9.03 (1H, s), 8.37 (1H, d, J 5.5 Hz), 7.76 (2H, d, J 8.4 Hz), 7.18-7.11 (3H, m), 5.39 (2H, s), 4.65-4.59 (1H, m), 3.83 (2H, q, J 7.1 Hz), 2.82, (3H, s), 2.59 (3H, s), 1.69-1.55 (3H, m), 1.02.(3H, t, J 7.1 Hz), 0.97 (3H, d, J 6.1 Hz), 0.95 (3H, d, J 6.2 Hz).

(i) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol

Lithium aluminium hydride (250 mg, 6.5 mmol) was added to a stirred solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester (2.0 g, 4.4 mmol) in dry THF (30 ml) under argon at room temperature. The reaction mixture was stirred overnight. Analysis by TLC (10% methanol in DCM) indicated that the reaction had not gone to completion. Additional lithium aluminium hydride (165 mg, 4.4 mmol) was added and the mixture stirred overnight. Water (0.5 ml) was added dropwise, followed by 15% aqueous sodium hydroxide (0.5 ml) and finally water (1.5 ml). The mixture was stirred for 0.5 h, filtered through celite and concentrated under reduced pressure. Chromatography (8-10% methanol in DCM) of the residue gave N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol (1.57 g, 89 %) as a colourless oil.

i.r. (KBr) 3252, 2954, 1331, 1151 cm^{-1}

δ_H 8.79 (1H, s), 8.16 (1H, d, J 5.6 Hz), 7.69 (2H, d, J 8.3 Hz), 7.08 (1H, br s), 7.04 (2H, d, J 8.7 Hz), 5.32 (2H, s), 4.05-3.90 (2H, m), 3.44-3.36 (2H, m), 2.61 (3H, s), 2.46 (3H, s), 1.40-1.27 (1H, m), 1.13-1.08 (2H, m), 0.72 (6H, d, J 6.5 Hz);

δ_C 153.66, 141.49, 141.07, 140.08, 140.02, 139.33, 139.22, 127.94, 126.49, 104.85, 62.10, 57.03, 46.63, 37.17, 28.01, 24.22, 22.60, 21.66.

Examples 2-21

The compounds of Examples 2-21 are prepared by the method of Example 1 employing the appropriate amino acid derivative *in lieu* of L-leucine ethyl ester hydrochloride in Step (b) and for certain compounds missing out the methylation Step (d) or employing a different alkyl halide *in lieu* of methyl iodide in Step (d).

2. N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

3. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D-leucinol

4. N-Ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

5. N-Allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

6. N-Propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

7. N-Benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

8. N-4-Methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol

9. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-isoleucinol

10. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-phenylalaninol

11. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-valinol

12. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-tryptophanol

13. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-methioninol

14. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-O-methyl-L-tyrosinol

15. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-norleucinol

16. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-phenylglycinol

17. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-t-butylglycinol

18. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-D,L-ethylglycinol

19. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-D,L-allylglycinol

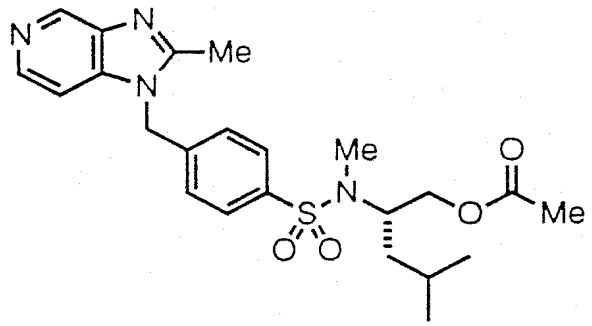
20. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-cyclopropylalaninol

21. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-cyclopentylalaninol

22. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-cyclohexylalaninol

Example 23

O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol



Acetic anhydride (1.6 ml, 17.4 mmol) was added slowly to a stirred solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol (350 mg, 0.86 mmol) in a stirred mixture of dry DCM (10 ml) and pyridine (16 ml) containing 4-dimethylaminopyridine (10 mg) at room temperature. The mixture was stirred overnight. DCM was added and the mixture washed with 10% aqueous citric acid, saturated aqueous sodium hydrogen carbonate, saturated aqueous copper sulphate, brine, dried, filtered and concentrated. Chromatography (7% methanol in DCM) of the residue gave O-ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol (76 mg, 20%) as a pale yellow oil.

i.r. (DCM) 2930, 1740, 1360, 1150 cm^{-1}

δ_H 9.03 (1H, s), 8.37 (1H, d, J 4.4 Hz), 7.73 (2H, d, J 7.6 Hz), 7.12 (3H, m), 5.37 (2H, s), 4.27-4.16 (1H, m), 3.96-3.82 (2H, m), 2.64 (3H, s), 2.56 (3H, s), 1.86 (3H, s), 1.47-1.36 (1H, m), 1.28-1.08.(2H, m), 0.82 (6H, d, J 6.5 Hz);

δ_C 170.38, 153.30, 141.93, 140.35, 139.52, 127.98, 126.65, 104.69, 63.16, 53.71, 46.67, 37.62, 28.07, 24.28, 22.81, 21.93, 20.60.

Examples 24-43

The compounds of Examples 24-43 are prepared by the method of Example 23 employing the appropriate N-substituted-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl amino acid alcohol derivative *in lieu* of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol.

24. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-D-leucinol

25. O-Ethanoyl-N-ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

26. O-Ethanoyl-N-allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

27. O-Ethanoyl-N-propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

28. O-Ethanoyl-N-benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

29. O-Ethanoyl-N-4-methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

30. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-isoleucinol

31. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-phenylalininol

32. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-valinol

33. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-tryptophanol

34. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-methioninol

35. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-O'-methyl-L-tyrosinol

36. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-norleucinol

37. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-phenylglycinol

38. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-t-butylglycinol

39. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-D,L-ethylglycinol

40. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-D,L-allylglycinol

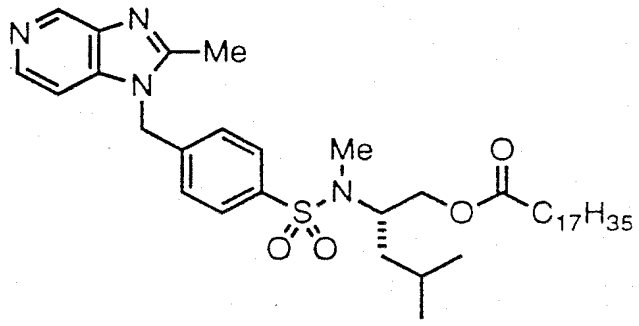
41. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclopropylalininol

42. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclopentylalininol

43. O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclohexylalininol

Example 44

O-Octadecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol



Stearoyl chloride (200 mg, 0.72 mmol) was added to a stirred solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol (300 mg, 0.72 mmol) and triethylamine (0.1 ml, 0.72 mmol) in dry THF (10 ml) at room temperature under argon. The mixture was stirred overnight and the solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated aqueous sodium hydrogen carbonate and brine, dried, filtered and concentrated. Chromatography (3% methanol in DCM) gave O-octadecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol (182 mg, 37%) as a white crystalline solid.

m.p. 59°C

i.r. ($CDCl_3$) 2930, 2850, 1725, 1340, 1160 cm^{-1}

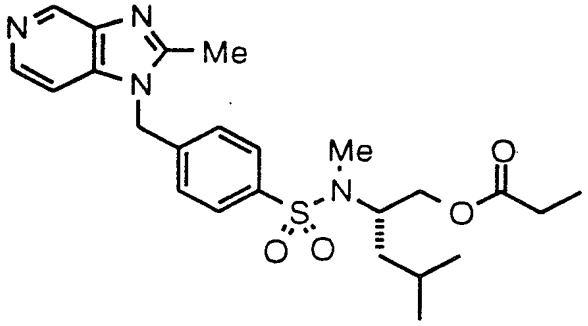
δ_H 8.97 (1H, s), 8.33 (1H, s), 7.71 (2H, d, J 8.3 Hz), 7.13 (1H, br s), 7.10 (2H, d, J 8.2 Hz), 5.34 (2H, s), 4.24-4.13 (1H, m), 3.96-3.81 (2H, m), 2.62 (3H, s), 2.53 (3H, s), 2.16 (2H, t, J 7.6 Hz), 1.65-1.03 (33H, m), 0.84-0.53 (9H, m);

δ_C 187.63, 176.58, 173.20, 153.53, 141.56, 141.37, 140.29, 139.46, 127.92, 126.66, 104.74, 63.19, 53.70, 46.70, 37.63, 33.93, 31.76, 29.52, 29.32, 29.20, 28.99, 28.23, 24.60, 24.28, 22.79, 22.53, 21.94, 13.96.

Examples 45-49

The compounds of Examples 45-49 were prepared by the method of Example 44 employing the appropriate acid chloride *in lieu* of stearoyl chloride.

45. O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol



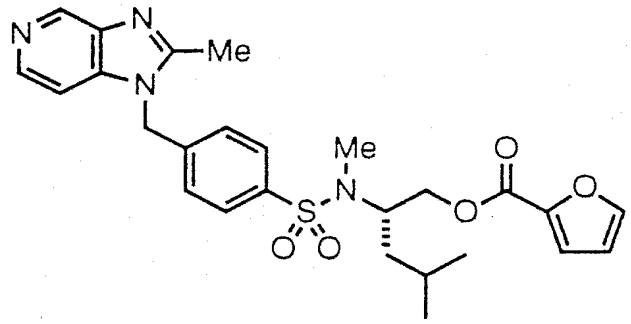
Yellow oil (38% yield after chromatography (5% methanol in DCM)):

i.r. ($CDCl_3$) 2960, 1735, 1340, 1155 cm^{-1}

δ_H 8.99 (1H, s), 8.33 (1H, br d), 7.73 (2H, d, J 8.3 Hz), 7.11 (3H, m), 5.37 (2H, s), 4.29-4.17 (1H, m), 4.00-3.85 (2H, m), 2.64 (3H, s), 2.55 (3H, s), 2.16 (2H, q, J 7.4 Hz), 1.50-1.32 (1H, m), 1.25-1.13 (2H, m), 1.03 (3H, t, J 7.5 Hz), 0.81 (6H, br d);

δ_C 173.62, 153.22, 142.10, 141.99, 140.56, 140.14, 139.59, 128.00, 126.68, 104.56, 63.25, 53.92, 46.74, 37.85, 28.26, 27.26, 24.41, 22.78, 22.03, 13.60.

46. O-2-Furoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol



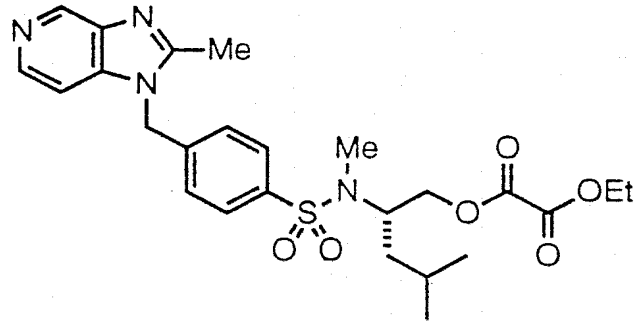
Yellow oil (22% yield after chromatography (5% methanol in DCM)):

i.r. ($CDCl_3$) 2960, 1720, 1340, 1180, 1120 cm^{-1}

δ_H 9.00 (1H, br s), 8.34 (1H, br s), 7.72 (2H, d, J 8.3 Hz), 7.45 (1H, d, J 1.8 Hz), 7.12-7.10 (2H, m), 7.00 (2H, d, J 8.2 Hz), 6.39 (1H, dd, J 3.6, 1.8 Hz), 5.32 (2H, s), 4.43-4.32 (1H, m), 4.20 (1H, dd, J 11.6, 7.9 Hz), 4.04 (1H, dd, J 11.7, 4.5 Hz), 2.67 (3H, s), 2.53 (3H, s), 1.53-1.17 (3H, m), 0.86 (3H, d, J 6.4 Hz), 0.85 (3H, d, J 6.6 Hz);

δ_C 158.07, 153.57, 146.53, 144.12, 141.68, 140.30, 139.51, 128.18, 126.62, 118.57, 111.97, 63.88, 53.93, 46.79, 37.87, 28.36, 24.44, 22.99, 22.03.

47. O-Ethyloxaloyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol



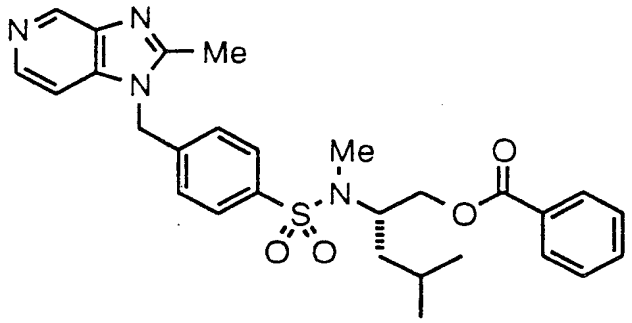
Pale yellow oil (29% yield after chromatography (3% methanol in DCM)):

i.r. ($CDCl_3$) 2960, 1780-1730, 1410-1350, 1130 cm^{-1}

δ_H 8.95 (1H, s), 8.29 (1H, d, J 5.6 Hz), 7.71 (2H, d, J 8.3 Hz), 7.12 (1H, s), 7.07 (2H, d, J 8.6 Hz), 5.34 (2H, s), 4.27-4.01 (3H, m), 4.21 (2H, q, J 7.1 Hz), 2.63 (3H, s), 2.52 (3H, s), 1.40-0.98 (6H, m), 0.79 (3H, d, J 6.4 Hz), 0.78 (3H, d, J 5.2 Hz);

δ_C 200.22, 177.61, 157.16, 156.88, 153.32, 141.89, 141.67, 140.06, 139.73, 139.63, 127.95, 126.67, 104.61, 65.91, 63.09, 53.23, 46.59, 37.41, 28.32, 24.18, 22.69, 21.78, 13.77.

48. O-Benzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol



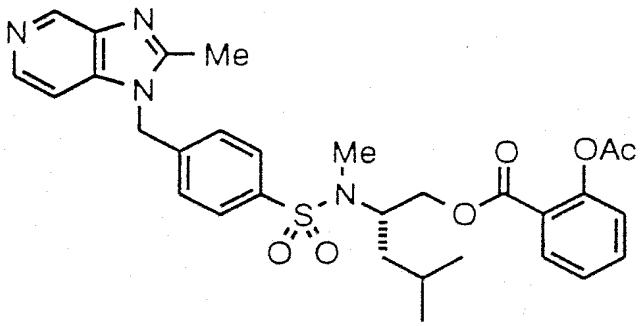
White foam (59% yield after chromatography (3-5% methanol in DCM)):

Analysis calculated for $C_{28}H_{32}N_4O_4S.0.6H_2O$
Requires C 63.28 H 6.30 N 10.54
Found C 63.21 H 6.24 N 10.38

i.r. ($CDCl_3$) 2960, 1725, 1615, 1275, 1160 cm^{-1}

δ_H 9.06 (1H, s), 8.39 (1H, d, J 5.5 Hz), 7.97 (2H, d, J 8.4 Hz), 7.77 (2H, d, J 8.2 Hz), 7.54 (1H, br dd), 7.39 (2H, dd, J 8.0, 7.4 Hz), 7.11 (1H, d, J 5.5 Hz), 7.00 (2H, d, J 8.2 Hz), 5.30 (2H, s), 4.49-4.42 (1H, m), 4.27 (1H, dd, J 11.7, 7.9 Hz), 4.13 (1H, dd, J 11.7, 4.5 Hz), 2.75 (3H, s), 2.56 (3H, s), 1.58-1.25 (3H, m), 0.93 (3H, d, J 6.4 Hz), 0.91 (3H, d, J 6.6 Hz).

49. O-2-Acetoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol



Yellow foam (22% yield after chromatography (5-8% methanol in DCM)):

i.r. ($CDCl_3$) 2960, 1760, 1725, 1340, 1180 cm^{-1}

δ_H 9.01 (1H, s), 8.34 (1H, d, J 5.2 Hz), 7.92 (1H, dd, J 7.8, 1.5 Hz), 7.71 (2H, d, J 8.2 Hz), 7.47 (1H, m), 7.20 (1H, m), 7.08 (1H, d, J 5.4 Hz), 7.02 (1H, d, J 8.1 Hz), 6.94 (2H, d, J 8.2 Hz), 5.26 (2H, s), 4.47-4.33 (1H, m), 4.15-4.01 (2H, m), 2.68 (3H, s), 2.50 (3H, s), 2.30 (3H, s), 1.58-1.20 (3H, m), 0.88 (3H, d, J 6.4 Hz), 0.86 (3H, d, J 6.6 Hz);

δ_C 169.38, 163.63, 153.32, 150.75, 141.95, 141.78, 140.17, 140.04, 139.54, 133.95, 131.48, 127.96, 126.65, 125.83, 123.67, 104.67, 64.04, 53.89, 46.64, 37.92, 28.26, 24.38, 22.88, 21.97, 20.89, 13.86.

Examples 50-77

The compounds of Examples 50-77 are prepared by the method of Example 44 employing the appropriate acid chloride *in lieu* of stearoyl chloride and for certain compounds the appropriate N-substituted-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl amino acid alcohol derivative was employed *in lieu* of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol.

50. O-Propanoyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol

51. O-Propanoyl-N-ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

52. O-Propanoyl-N-allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

53. O-Propanoyl-N-methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

54. O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-isoleucinol

55. O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclopentylalininol

56. O-Butanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

57. O-Pentanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

58. O-Hexanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

59. O-Octanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

60. O-Decanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

61. O-Dodecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol

62. O-Tetradecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

63. O-Hexadecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

64. O-2-Thiophenecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

65. O-2-Tetrahydrofuroyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

66. O-2-Pyridinecarbonyl-N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

67. O-3-Pyridinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

68. O-4-Pyridinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

69. O-3-Quinolinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

70. O-2-Trifluoromethylbenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

71. O-2-Bromobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

72. O-3-Chlorobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

73. O-4-Methoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

74. O-4-Fluorobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

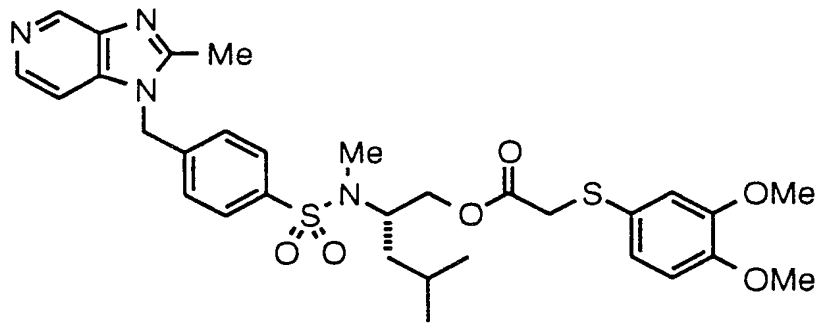
75. O-3,4-Dimethoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

76. O-3-Chloro-4-methoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

77. O-2,2-Dimethylpropanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

Example 78

O-2-(3,4-Dimethoxyphenylmercapto)ethanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol



(a) Pentafluorophenyl 2-(3,4-dimethoxyphenylmercapto)ethanoate

A solution of 2-(3,4-dimethoxyphenylmercapto)ethanoic acid (1.71 g, 7.5 mmol), N-methylmorpholine (0.99 ml, 9.0 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.87 g, 9.7 mmol) and pentafluorophenol (2.76 g, 15.0 mmol) in DCM (100 ml) was stirred at room temperature overnight. The solution was washed with 2M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, dried, filtered and concentrated to give crude pentafluorophenyl 2-(3,4-dimethoxyphenylmercapto)ethanoate (2.95 g, 99%) as pink oil which was used directly in the next step.

δ_H 7.16 (1H, dd, J 8.3, 2.2 Hz), 7.09 (1H, d, J 2.1 Hz), 6.85 (1H, d, J 8.3 Hz), 3.89 (6H, s), 3.81 (2H, s).

(b) O-2-(3,4-Dimethoxyphenylmercapto)ethanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

A mixture of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol (3.12 g, 7.5 mmol), pentafluorophenyl 2-(3,4-dimethoxyphenylmercapto)ethanoate (2.95 g, 7.4 mmol) and 4-N,N-dimethylaminopyridine (20 mg) in DCM (100 ml) was heated at reflux overnight. The mixture was cooled, washed with saturate aqueous sodium hydrogen carbonate and brine, dried, filtered and evaporated. Chromatography (4-6% methanol in DCM) gave O-2-(3,4-dimethoxyphenylmercapto)ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol (4.46 g, 95%) as a white foam.

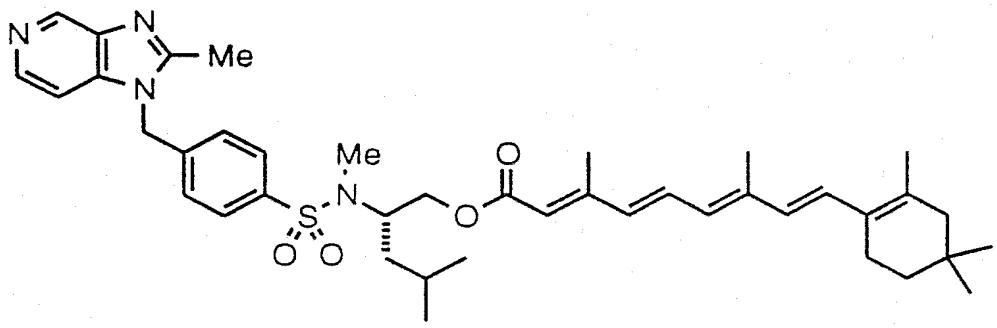
i.r. ($CDCl_3$) 1735, 1610, 1585 cm^{-1}

δ_H 9.03 (1H, s), 8.35 (1H, d, J 5.5 Hz), 7.75 (2H, d, J 8.3 Hz), 7.14-7.11 (3H, m), 7.00-6.97 (2H, m), 6.77 (1H, dd, J 7.1, 1.9 Hz), 5.38 (2H, s), 4.27-4.16 (1H, m), 4.02-3.88 (2H, m), 3.85 (3H, s), 3.84 (3H, s), 3.39 (2H, s), 2.64 (3H, s), 2.58 (3H, s), 1.45-1.34 (1H, m), 1.27-1.07 (2H, m), 0.81 (6H, d, J 6.6 Hz);

δ_C 169.47, 153.25, 149.09, 142.14, 142.02, 140.33, 140.11, 139.76, 139.64, 128.05, 126.68, 125.12, 124.59, 115.07, 111.56, 104.58, 64.32, 55.93, 55.86, 53.62, 46.70, 37.90, 37.56, 28.23, 24.29, 22.61, 21.94, 13.69.

Example 79

O-Retinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol



O-Retinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol was prepared by the procedure of Example 78 employing retinoic acid *in lieu* of 2-(3,4-dimethoxyphenylmercapto)ethanoic acid as starting material.

Yellow foam (69% yield after chromatography (5% methanol in DCM)):

i.r. (DCM) 2925, 1710, 1610, 1570, 1340, 1145 cm^{-1}

δ_H 9.06 (1H, s), 8.42 (1H, d, J 5.9 Hz), 7.84 (2H, d, J 8.3 Hz), 7.33 (1H, d, J 5.9 Hz), 7.35-7.32 (2H, m), 7.04 (1H, dd, J 15.0, 11.4 Hz), 6.39-6.13 (4H, m), 5.61 (1H, s), 5.46 (2H, s), 4.36-4.25 (1H, m), 4.00-3.87 (2H, m), 2.73 (3H, s), 2.65 (3H, s), 2.33 (3H, s), 2.03 (3H, s), 2.05-1.95 (2H, m), 1.72 (3H, s), 1.68-1.23 (7H, m), 1.04 (6H, s), 0.92 (3H, d, J 6.4 Hz), 0.91 (3H, d, J 6.6 Hz);

δ_C (major signals) 117.45, 104.86, 63.01, 54.02, 46.85, 39.53, 37.92, 34.20, 33.05, 28.91, 28.46, 24.38, 23.00, 22.00, 21.69, 19.15, 13.92, 13.87, 12.91.

Examples 80-85

The compounds of Examples 80-85 are prepared by the method of Example 78 employing the appropriate carboxylic acid *in lieu* of 2-(3,4-dimethoxyphenylmercapto)ethanoic acid and N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol as starting material.

80. O-2-(4-Methoxyphenyl)ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

81. O-2-(3,4-Dimethoxyphenyl)ethanoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

82. O-3-(4-Methoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

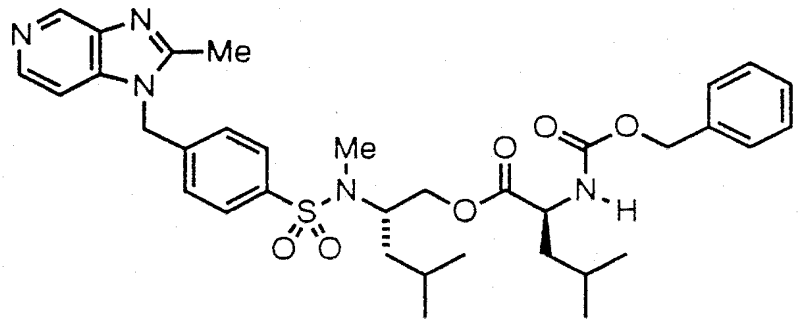
83. O-3-(3,4-Dimethoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

84. O-3-(3-Chloro-4-methoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

85. O-3-(Pyridin-3-yl)propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

Example 86

O-(N'-Benzyloxycarbonyl)-L-leucinoyl-N-Methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol



A mixture of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol (350 mg, 0.86 mmol), N-benzyloxycarbonyl-L-leucine p-nitrophenyl ester (332 mg, 0.86 mmol) and imidazole (20 mg) in dry DCM (10 ml) was heated at reflux for 48 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed with 10% aqueous potassium carbonate and brine, dried, filtered and concentrated. Chromatography (7% methanol in DCM) of the residue gave O-(N'-benzyloxycarbonyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol (290 mg, 51%) as a white foam.

i.r. (DCM) 2930, 1740, 1725, 1340, 1150 cm^{-1}

δ_H 9.05 (1H, s), 8.39 (1H, d, J 5.4 Hz), 7.78 (2H, d, J 7.5 Hz), 7.37-7.30 (5H, m), 7.21 (1H, d, J 5.6 Hz), 7.15 (2H, d, J 8.3 Hz), 5.41-5.33 (3H, m), 5.12 (2H, s), 4.29-4.21 (2H, m), 4.08 (1H, dd, J 11.6, 4.8 Hz), 3.89 (1H, dd, J 11.6, 8.2 Hz), 2.67 (3H, s), 2.60 (3H, s), 1.68-1.56 (2H, m), 1.52-1.39.(2H, m), 1.25-1.19 (2H, m), 0.92 (6H, br d, J 7.3 Hz), 0.87 (6H, br d, J 5.7 Hz);

δ_C 172.46, 155.97, 153.54, 141.85, 141.74, 140.36, 140.21, 139.75, 136.36, 128.45, 128.07, 127.90, 126.81, 104.77, 66.84, 63.98, 53.59, 52.55, 46.79, 41.51, 37.71, 28.26, 24.66, 24.40, 22.84, 22.76, 22.06, 21.81.

Examples 87-95

The compounds of Examples 87-95 are prepared by the method of Example 86 employing the appropriate amino acid derivative *in lieu* of N-benzyloxycarbonyl-L-leucine p-nitrophenyl ester.

87. O-(N',N'-Dibenzyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

88. O-(N'-Benzyloxycarbonyl)glycinoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

89. O-(N'-Benzyloxycarbonyl)-D-leucinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

90. O-(N'-Benzyloxycarbonyl)-L-phenylalininoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

91. O-(N',N'-dibenzyl)glycinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

92. O-(N'-Benzyloxycarbonyl)-L-norleucinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

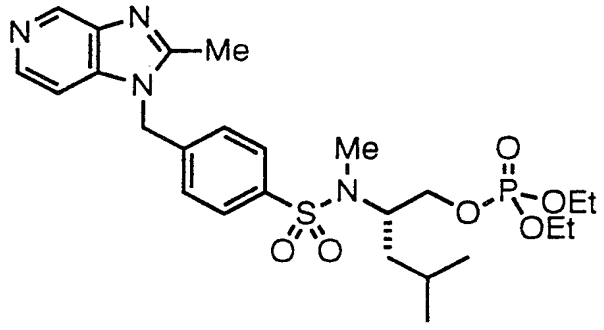
93. O-(N'-Butoxycarbonyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

94. O-(N'-Benzyloxycarbonyl)-L-valinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

95. O-(N'-Benzyloxycarbonyl)-L-phenylglycinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

Example 96

O-Diethoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol



O-Diethoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol was prepared by the method of Example 44 employing diethyl chlorophosphate *in lieu* of stearoyl chloride.

Pale yellow oil (13% yield after chromatography (3-7% methanol in DCM)):

i.r. ($CDCl_3$) 2960, 1610, 1345, 1180 cm^{-1}

δ_H 9.01 (1H, s), 8.35 (1H, d, J 5.3 Hz), 7.77 (2H, d, J 8.3 Hz), 7.16-7.11 (3H, m), 5.38 (2H, s), 4.27-4.16 (1H, m), 4.09-3.97 (4H, m), 3.87 (1H, d, J 5.8 Hz), 3.84 (1H, d, J 5.8 Hz), 2.68 (3H, s), 2.57 (3H, s), 2.49-1.33 (1H, m), 1.28-1.17 (8H, m), 0.84 (6H, d, J 6.5 Hz);

δ_C 153.32, 142.06, 141.93, 140.15, 140.05, 139.77, 139.61, 128.12, 126.65, 104.65, 67.05, 66.96, 63.90, 63.81, 54.73, 54.60, 46.73, 37.16, 28.45, 24.26, 22.88, 21.91, 16.06, 15.96.

Examples 97-99

The compounds of Examples 97-99 are prepared by the method of Example 96 employing the appropriate chlorophosphate derivative *in lieu* of diethyl chlorophosphate.

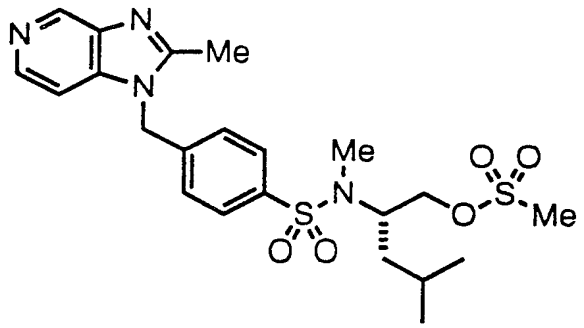
97. O-Dimethoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

98. O-Diphenoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

99. O-Diisopropoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

Example 100

O-Methylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol



O-Methylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol was prepared by the method of Example 44 employing methanesulphonyl chloride *in lieu* of stearoyl chloride.

White foam (61% yield after chromatography (3% methanol in DCM)):

i.r. ($CDCl_3$) 2960, 1615, 1360 cm^{-1}

δ_H 9.05 (1H, s), 8.39 (1H, d, J 5.5 Hz), 7.80 (2H, d, J 8.4 Hz), 7.17-7.14 (3H, m), 5.40 (2H, s), 4.34-4.28 (1H, m), 4.09-4.02 (2H, m), 2.90 (3H, s), 2.72 (3H, s), 2.60 (3H, s), 1.53-1.15 (3H, m), 0.89 (6H, d, J 6.5 Hz);

δ_C 153.36, 142.16, 142.04, 140.18, 139.90, 128.16, 126.78, 104.68, 68.34, 53.90, 46.77, 37.29, 30.87, 28.39, 24.33, 22.92, 21.85.

Examples 101-104

The compounds of Examples 101-104 are prepared by the method of Example 100 employing the appropriate sulphonyl chloride derivative *in lieu* of methanesulphonyl chloride.

101. O-Ethylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

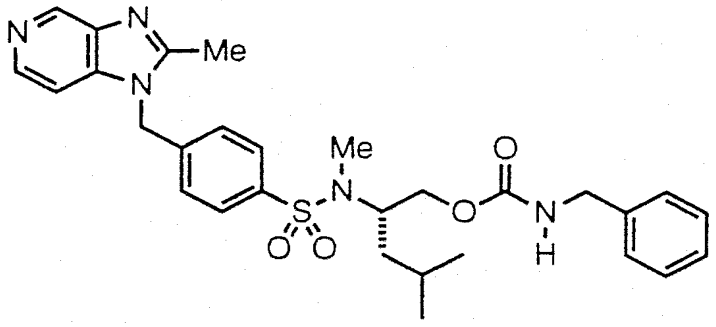
102. O-Propylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

103. O-Phenylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol

104. O-4-Methylphenylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

Example 105

O-Benzylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)-L-leucinol



(a) Dipyrid-2-ylcarbonate

Triethylamine (10.5 ml, 75 mmol) was added slowly to a solution of triphosgene (3.0 g, 10 mmol) and 2-hydroxypyridine (5.7 g, 60 mmol) in dry DCM (500 ml) at 0°C under argon. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (500 ml), washed with saturated aqueous sodium hydrogen carbonate (2x150 ml) and brine (200 ml), dried, filtered and concentrated to give an orange oil. Crystallisation from ethyl acetate/hexane gave dipyrid-2-ylcarbonate as an off-white crystalline solid (3.70 g, 57%).

δ_H 8.42 (2H, dd, J 4.8, 1.1 Hz), 7.83 (2H, ddd, J 7.8, 7.7, 1.8 Hz), 7.30-7.23 (4H, m).

(b) O-Pyridin-2-yloxycarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

Dipyrid-2-ylcarbonate (234 mg, 1.1 mmol) was added to a stirred solution of triethylamine (100 µl, 1.1 mmol) and N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol (300 mg, 0.7 mmol) in dry DCM (5 ml) at room temperature under argon. The mixture was stirred overnight, DCM (40 ml) added and the solution washed with saturated aqueous sodium hydrogen carbonate and brine. The organics were dried, filtered and

concentrated to give crude O-pyridin-2-yloxycarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol (366 mg, 95%) as a white foam, which was used directly in the next step.

δ_H 8.97 (1H, s), 8.36-8.29 (2H, m), 7.86-7.77 (3H, m), 7.29-7.23 (1H, m), 7.17-7.05 (4H, m), 5.36 (2H, s), 4.45-4.33 (1H, m), 4.09-4.06 (2H, m), 3.46 (3H, s), 2.72 (3H, s), 1.63-1.46 (1H, m), 1.42-1.16 (2H, m), 0.90 (6H, d, J 6.5 Hz).

(c) O-Benzylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

A solution of O-pyridin-2-yloxycarbonyl-(N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl)-L-leucinol (366 mg, 0.7 mmol) in dry DCM (2 ml) was added to a stirred solution of benzylamine (90 µl, 0.8 mmol) in dry DCM (5 ml) at room temperature under argon. The mixture was stirred overnight, DCM (40 ml) added and the solution washed with 10% aqueous citric acid. The organics were concentrated under reduced pressure and the residue partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic phase was washed with brine, dried, filtered and evaporated to give a yellow foam. Chromatography (5% methanol in DCM) gave O-benzylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol (140 mg, 37%) as a colourless oil.

i.r. ($CDCl_3$) 3450, 1725, 1340, 1150 cm^{-1}

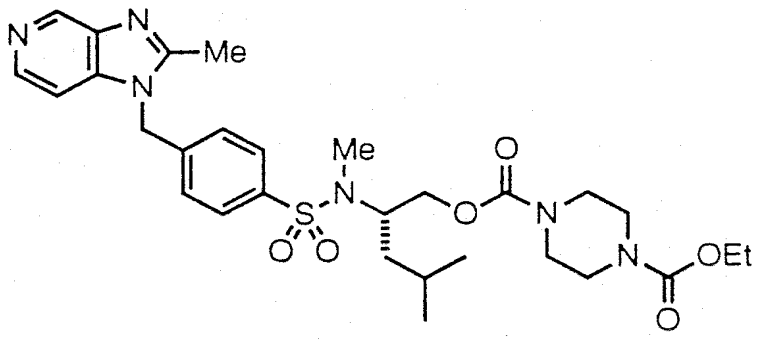
δ_H 8.96 (1H, s), 8.30 (1H, d, J 5.6 Hz), 7.73 (2H, d, J 8.2 Hz), 7.32-7.21 (5H, m), 7.08-7.05 (1H, m), 7.06 (2H, d, J 8.3 Hz), 5.49-5.15 (1H, m), 5.25 (2H, s), 4.28-4.20 (1H, m), 4.27 (2H, d, J 5.9 Hz), 3.92 (2H, d, J 6.5 Hz), 2.63 (3H, s), 2.51 (3H, s), 1.50-1.30 (1H, m), 1.30-1.05 (2H, m), 0.83 (3H, d, J 6.1 Hz), 0.82 (3H, d, J 6.4 Hz);

δ_C 155.86, 153.57, 141.58, 141.41, 140.31, 139.66, 139.42, 138.22, 128.56, 128.06, 127.42, 127.30, 104.73, 63.69, 54.09, 46.64, 44.88, 37.46, 28.04, 24.29, 22.88, 21.93.

Example 106-109

The compounds of Examples 106-109 were prepared by the procedure of Example 105 employing the appropriate amine.

106. O-4-Ethoxycarbonylpiperazinecarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol



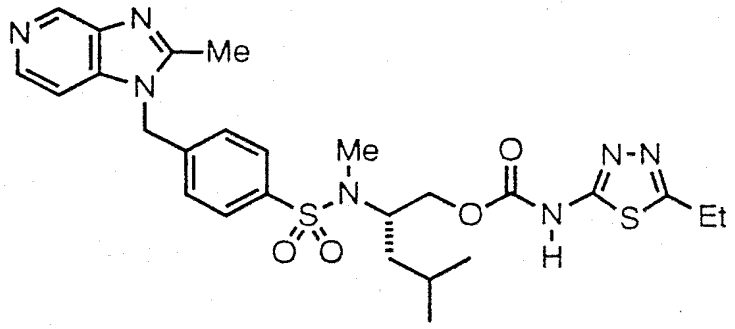
Colourless oil (14% yield after chromatography (5% methanol in DCM)):

i.r. ($CDCl_3$) 3330, 2930, 1715-1650, 1420-1335, 1110-1080 cm^{-1}

δ_H 9.01 (1H, s), 8.34 (1H, d, J 5.6 Hz), 7.74 (2H, d, J 8.3 Hz), 7.14-7.10 (3H, m), 5.38 (2H, s), 4.34-4.23 (1H, m), 4.11 (2H, q, J 7.0 Hz), 3.98 (2H, d, J 7.1 Hz), 3.45 (8H,s), 2.61 (3H, s), 2.56 (3H, s), 1.96-1.34 (1H, m), 1.22 (3H, t, J 7.2 Hz), 1.12 (2H, dd, J 7.0, 6.8 Hz), 0.80 (3H, d, J 6.3 Hz), 0.79 (3H, d, J 6.4 Hz);

δ_C 155.28, 154.60, 153.26, 142.00, 141.87, 140.42, 140.11, 139.73, 139.52, 127.87, 126.65, 104.56, 63.57, 61.41, 54.01, 46.69, 43.50, 43.27, 37.36, 27.76, 24.41, 22.75, 22.10, 14.51.

107. O-5-Ethyl-1,3,4-thiadiazol-2-ylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol



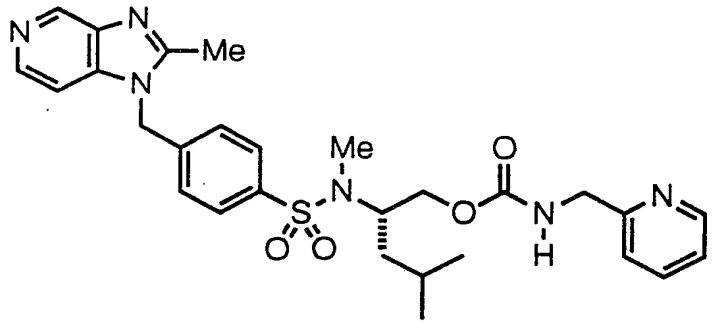
White foam (1% yield after chromatography (5-8% methanol in DCM)):

i.r. ($CDCl_3$) 3370, 2960, 1735-1715, 1430, 1140 cm^{-1}

δ_H 8.96 (1H, s), 8.60 (1H, d, J 5.7 Hz), 7.78 (2H, d, J 8.3 Hz), 7.69 (1H, d, J 5.6 Hz), 6.94 (2H, d, J 8.3 Hz), 5.42, 5.39 (2H, 2s), 4.49-4.37 (1H, m), 4.23 (1H, dd, J 11.7, 10.6 Hz), 4.03 (1H, dd, J 11.8, 4.0 Hz), 3.08 (2H, q, J 7.6 Hz), 2.89 (3H, s), 2.46 (3H, s), 1.80-1.66 (1H, m), 1.51-1.39 (1H, m), 1.44 (3H, t, J 7.6 Hz), 1.26-1.14 (1H, m), 1.00 (3H, d, J 6.3 Hz), 0.98 (3H, d, J 6.6 Hz);

δ_C 167.01, 160.68, 154.69, 152.79, 141.54, 141.31, 140.75, 140.00, 139.79, 105.87, 65.16, 54.50, 47.07, 37.84, 28.22, 24.50, 23.64, 23.05, 22.16, 14.01.

108. O-Pyridin-2-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol



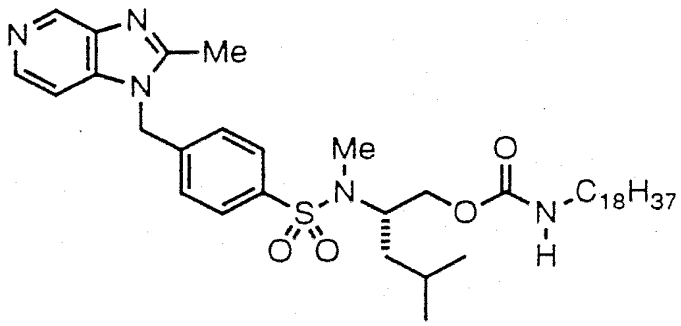
White foam (61% yield after chromatography (5-10% methanol in DCM)):

i.r. ($CDCl_3$) 3665, 3630, 2960, 1735-1690, 1345, 1175 cm^{-1}

δ_H 8.93 (1H, s), 8.45 (1H, dd, J 4.8, 1.0 Hz), 8.28 (1H, d, J 5.6 Hz), 7.74 (2H, d, J 8.2 Hz), 7.62 (1H, ddd, J 7.7, 7.6, 1.6 Hz), 7.23 (1H, d, J 7.8 Hz), 7.17-7.08 (4H, m), 5.87-5.83 (1H, m), 5.34 (2H, s), 4.35 (2H, dd, J 5.7, 5.5 Hz), 4.28-4.17 (1H, m), 3.90 (2H, d, J 6.3 Hz), 2.63 (3H, s), 2.51 (3H, s), 1.49-1.41 (1H, m), 1.23-1.10 (2H, m), 0.83 (3H, d, J 6.3 Hz), 0.82 (3H, d, J 6.6 Hz);

δ_C 156.63, 155.88, 153.44, 148.85, 141.63, 141.59, 140.24, 140.14, 139.57, 139.46, 136.80, 128.07, 126.60, 122.37, 121.69, 104.67, 63.65, 54.14, 50.18, 46.66, 45.81, 37.50, 28.02, 24.26, 22.67, 21.90.

109. O-Octadecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol



Colourless oil (5% yield after chromatography (3% methanol in DCM)):

i.r. ($CDCl_3$) 3440, 2920, 1710, 1335, 1140 cm^{-1}

δ_H 9.04 (1H, s), 8.37 (1H, d, J 5.6 Hz), 7.78 (2H, d, J 8.4 Hz), 7.14 (3H, m), 5.39 (2H, s), 4.74-4.65 (1H, m), 4.27-4.22 (1H, m), 3.90 (2H, d, J 6.5 Hz), 3.13-3.04 (2H, m), 2.64 (3H, s), 2.58 (3H, s), 1.46-1.35 (3H, m), 1.33-1.10 (32H, m), 0.87-0.83 (9H, m);

δ_C 155.88, 153.32, 142.08, 141.98, 140.20, 139.48, 128.17, 126.65, 104.59, 63.47, 54.14, 46.79, 41.06, 37.54, 31.86, 29.89, 29.63, 29.29, 29.23, 28.13, 26.67, 24.40, 22.95, 22.63, 22.02, 14.05.

Example 110-130

The compounds of Examples 110-130 are prepared by the procedure of Example 105 employing the appropriate amine.

110. O-Methylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

111. O-Ethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

112. O-n-Propylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

113. O-i-Propylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

114. O-n-Pentylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

115. O-n-Hexylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

116. O-n-Octylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

117. O-n-Decylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

118. O-n-Dodecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

119. O-n-Tetradecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

120. O-n-Hexadecylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

121. O-t-Butylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

122. O-Pyridin-2-ylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol

123. O-Pyridin-4-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

124. O-Pyridin-3-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

125. O-4-Methoxyphenylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

126. O-3,4-Dimethoxybenzylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

127. O-2-(4-Methoxyphenyl)ethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

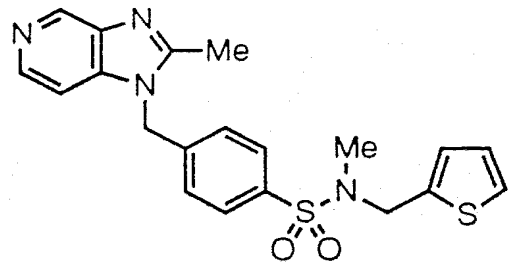
128. O-2-(3,4-Dimethoxyphenyl)ethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

129. O-3-(3,4-Dimethoxyphenyl)propylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

130. O-3-(Pyridin-3-yl)propylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol

Example 131

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-thienylmethylamine



(a) 4-Bromomethylphenylsulphonyl-2-thienylmethylamine

4-Bromomethylphenylsulphonyl-2-thienylmethylamine was prepared by the procedure of Example 1 Step (b) employing 2-thienylmethylamine *in lieu* of L-leucine ethyl ester hydrochloride.

Yellow amorphous solid (66% yield after chromatography (1:3 ethyl acetate/hexane)):

δ_H 7.85 (2H, d, J 8.3 Hz), 7.54 (2H, dd, J 8.3 Hz), 7.21 (1H, d, J 4.7 Hz), 6.91-6.87 (2H, m), 4.75 (1H, br s), 4.51 (2H, s), 4.39 (2H, d, J 5.7 Hz).

(b) N-Methyl 4-bromomethylphenylsulphonyl-2-thienylmethylamine

A mixture of 4-bromomethylphenylsulphonyl-2-thienylmethylamine (10.0 g, 28.9 mmol), dimethylsulphate (2.75 ml, 28.9 mmol) and potassium carbonate (19.96 g, 144 mmol) in acetone (100 ml) was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate, washed with water and brine, dried, filtered and evaporated. Chromatography of the residue (1:2 ethyl acetate/hexane) gave N-

methyl 4-bromomethylphenylsulphonyl-2-thienylmethylamine (1.60 g, 15%) as a colourless oil which was used directly in the next step.

(c) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-thienylmethylamine

A suspension of potassium hydroxide (0.60 g, 10.0 mmol), TDA-1 (4 drops) in dry acetonitrile (20 ml) was stirred for 10 min. at room temperature under argon. 2-Methylimidazo[4,5-c]pyridine (0.60 g, 4.4 mmol) was added and the reaction mixture was heated at 80°C for 40 min and cooled to 40°C. A solution of N-methyl 4-bromomethylphenylsulphonyl-2-thienylmethylamine (1.6 g, 4.4 mmol) in dry acetonitrile (10 ml) was added and the reaction mixture stirred at 40°C overnight and cooled to room temperature. The solvent was removed and the residue taken up in ethyl acetate, washed with brine, dried, filtered and concentrated. Column chromatography (6% methanol in DCM) gave N-methyl-N-4-(3H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-thienylmethylamine (0.17 g, 9%), N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-thienylmethylamine (0.21 g, 12%) and N-methyl-N-4-(5H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-thienylmethylamine. The 3H- and 5H-regioisomers, although not claimed in this patent application, are antagonists of platelet activating factor. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-thienylmethylamine was obtained as a yellow oil.

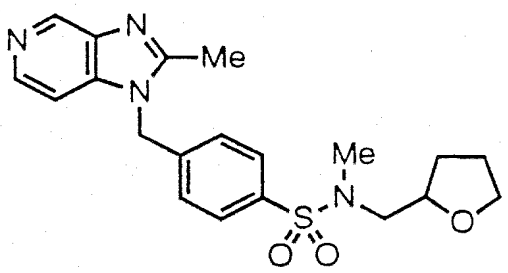
i.r. ($CDCl_3$) 2210, 1610, 1350, 1160 cm^{-1}

δ_H 9.02 (1H, s), 8.37 (1H, s), 7.71 (2H, d, J 8.3 Hz), 7.16 (4H, m), 6.86 (2H, m), 5.39 (2H, s), 4.35 (2H, s), 2.66 (3H, s), 2.58 (3H, s);

δ_C 153.29, 141.86, 141.63, 140.01, 139.92, 137.70, 137.60, 127.96, 127.24, 126.80, 126.55, 125.99, 104.65, 48.48, 46.57, 33.99.

Example 132

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-tetrahydrofurfurylamine



N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-tetrahydrofurfurylamine was prepared by the procedure of Example 131 employing tetrahydrofurfurylamine *in lieu* of 2-thienylmethylamine.

Yellow foam (10% yield for last step after chromatography (5% methanol in DCM)):

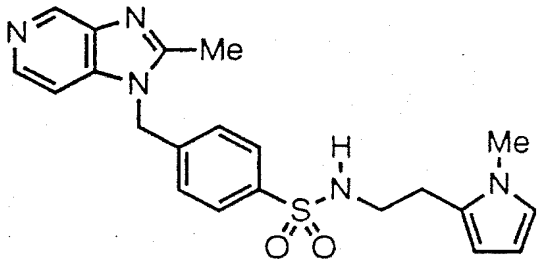
i.r. ($CDCl_3$) 2860, 1600, 1340, 1150 cm^{-1}

δ_H 8.52 (1H, s), 8.33 (1H, s), 7.61 (2H, d, J 8.2 Hz), 7.53 (1H, d, J 3.9 Hz), 7.11 (2H, d, J 8.3 Hz), 5.39 (2H, s), 3.95-3.87 (1H, m), 3.74-3.55 (2H, m), 3.08 (1H, dd, J 13.8, 4.2 Hz), 2.83 (1H, dd, J 13.9, 6.6 Hz), 2.72 (3H, s), 2.53 (3H, s), 1.91-1.72 (3H, m), 1.62-1.52 (1H, m);

δ_C 154.95, 147.63, 142.07, 139.67, 132.79, 132.17, 127.93, 126.71, 113.83, 77.55, 67.91, 53.48, 46.79, 36.05, 28.79, 25.19.

Example 133

N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-(N'-methylpyrrol-2-yl)ethylamine



N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-(N'-methylpyrrol-2-yl)ethylamine was prepared by the procedure of Example 131 Steps (a) and (c) employing (N'-methylpyrrol-2-yl)ethylamine as starting material *in lieu* of 2-thienylmethylamine.

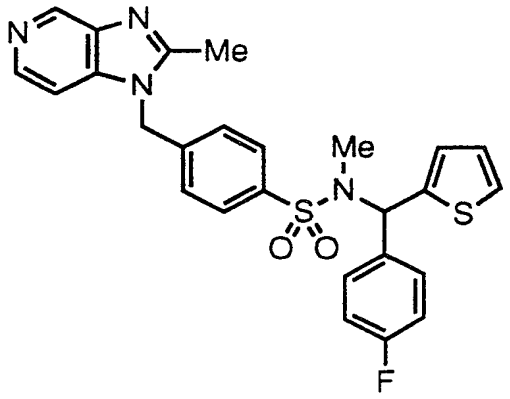
Yellow oil (0.3% yield for last step after chromatography (8% methanol in DCM)):

i.r. ($CDCl_3$) 1605, 1510, 1340, 1230, 1160, 985 cm^{-1}

δ_H 9.04 (1H, s), 8.40 (1H, s), 7.79 (2H, d, J 8.3 Hz), 7.20 (1H, s), 7.16 (2H, d, J 8.4 Hz), 6.51-6.50 (1H, m), 6.00 (1H, t, J 3.1 Hz), 5.77 (1H, dd, J 3.4, 1.8 Hz), 5.42 (2H, s), 5.08 (1H, t, J 6.3 Hz), 3.45 (3H, s), 3.22-3.14 (2H, m), 2.76 (2H, t, J 6.8 Hz), 2.01 (3H, s).

Example 134

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(4-fluorophenyl)-1-(2-thienyl)methylamine



(a) (4-Fluorophenyl)-(2-thienyl)methanol

Lithium aluminium hydride (3.68 g, 97 mmol) was added portionwise to a stirred solution of (4-fluorophenyl)-(2-thienyl)ketone (10.0 g, 48.5 mmol) in dry THF (160 ml) at room temperature under argon. The mixture was stirred overnight and water (3.7 ml) added dropwise with caution. After 0.5 h 15% aqueous sodium hydroxide (3.7 ml) was added and the mixture stirred for 0.5 h, finally water (11 ml) was added and the mixture stiired for 0.5 h. The precipitate was removed by filtration through celite and the filtrate was concentrated under reduced pressure to give (4-fluorophenyl)-(2-thienyl)-methanol (10.0 g, 99%) as a yellow oil.

δ_H 7.45-7.39 (2H, m), 7.28 (1H, dd, J 5.1, 1.1 Hz), 7.09-7.02 (2H, m), 6.96 (1H, dd, J 5.1, 3.5 Hz), 6.90-6.88 (1H, m), 6.04 (1H, s), 2.62 (1H, br s).

(b) (4-Fluorophenyl)-(2-thienyl)methylamine

A solution of diethyl azodicarboxylate (4.20 g, 24 mmol) in dry THF (20 ml) was added dropwise to a stirred mixture of (4-fluorophenyl)-(2-thienyl)methanol (5.0 g, 24 mmol), phthalamide (3.53 g, 24 mmol) and triphenyl phosphine (6.3 g, 24 mmol) in dry THF (60 ml) at room temperature under argon. The reaction mixture was stirred overnight and the solvent removed under reduced pressure. Diethyl ether was added and the mixture was placed in the refridgerator overnight. The precipitate that formed was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (160 ml) and hydrazine hydrate (1.20 g, 24 mmol) was added and the resulting mixture heated at reflux for 2 h. Concentrated hydrochloric acid was added dropwise until a precipitate formed and the mixture was filtered. The filtrate was concentrated under reduced pressure and taken up in ethyl acetate, 1M sodium hydroxide added and the organic layer separated. The aqueous layer was extracted with ether and the organics were combined and concentrated under reduced pressure to give a brown oil. Chromatography (1% methanol in DCM) gave (4-fluorophenyl)-(2-thienyl)methylamine (2.4 g, 48%).

δ_H 7.44-7.36 (2H, m), 7.22 (1H, dd, J 5.1. 1.0 Hz), 7.08-7.00 (2H, m), 6.95 (1H, dd, J 5.0, 3.5 Hz), 6.85 (1H, dd, J 3.4, 0.9 Hz), 5.42 (1H, s), 2.11 (2H, s).

(c) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(4-fluorophenyl)-1-(2-thienyl)methylamine

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(4-fluorophenyl)-1-(2-thienyl)methylamine was prepared by the procedure of Example 131 employing (4-fluorophenyl)-(2-thienyl)methylamine as starting material.

Yellow amorphous solid (3% yield for the last step after chromatography (4% methanol in DCM) to separate the desired 1H-regioisomer from the 3H- and 5H-regioisomers):

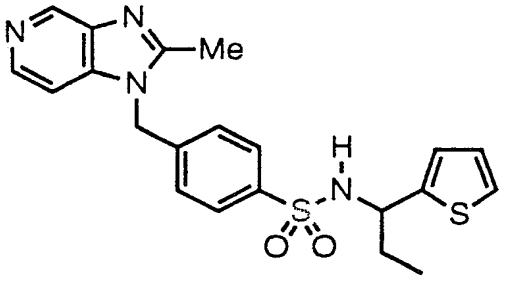
i.r. ($CDCl_3$) 1605, 1510, 1340, 1230, 1160, 985 cm^{-1}

δ_H 9.06 (1H, br s), 8.50 (1H, br s), 7.67 (2H, d, J 8.2 Hz), 7.28-7.20 (3H, m), 7.11-7.06 (3H, m), 7.01-6.94 (2H, m), 6.85-6.82 (1H, m), 6.68 (1H, br s), 6.58 (1H, s), 5.37 (2H, s), 2.72 (3H, s), 2.59 (3H, s);

δ_C 164.27, 160.32, 154.60, 140.99, 140.63, 140.13, 139.35, 139.30, 133.62, 129.89, 129.76, 128.05, 127.91, 126.71, 126.56, 125.65, 115.45, 115.10, 59.75, 47.01, 30.65, 14.05.

Example 135

N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)propylamine



N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)-propylamine was prepared by the procedures of Example 134 Steps (a) and (b) and Example 131 Steps (a) and (c) employing ethyl-(2-thienyl)ketone as starting material.

White crystalline solid (4% yield for the last step after chromatography (5-8% methanol in DCM) to separate the desired 1H-regioisomer from the 3H- and 5H-regioisomers): m.p. 185-186°C

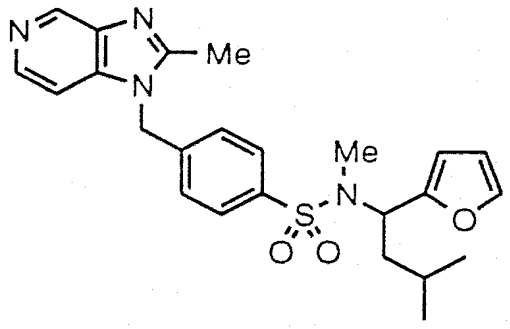
i.r. ($CDCl_3$) 1610, 1410, 1340, 1160, 1030 cm^{-1}

δ_H 9.00 (1H, s), 8.38 (1H, d, J 5.6 Hz), 7.63 (2H, d, J 8.3 Hz), 7.14 (1H, d, J 5.7 Hz), 6.99 (2H, d, J 8.3 Hz), 6.92 (1H, dd, J 3.4, 3.1 Hz), 6.67-6.64 (2H, m), 6.09 (1H, d, J 8.0 Hz), 5.33 (2H, s), 4.54 (1H, dt, J 7.5, 7.3 Hz), 2.57 (3H, s), 1.92-1.77 (2H, m), 0.86 (3H, t, J 7.3 Hz);

δ_C 153.69, 144.75, 141.42, 141.35, 141.15, 140.20, 139.52, 138.86, 127.46, 126.40, 126.12, 124.76, 124.23, 104.93, 55.15, 46.70, 31.08, 10.48.

Example 136

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-furyl)-3-methylbutylamine



(a) 1-(2-Furyl)-3-methylbutanol

Furan was added dropwise to a stirred solution of n-butyllithium (2.5 M in hexanes, 58.8 ml, 147 mmol) in dry THF (200 ml) at -20°C under argon. The mixture was allowed to warm to room temperature and was then heated at reflux for 4 h. The mixture was cooled to -30°C and isovaleraldehyde (12.8 g, 147 mmol) was added dropwise. The mixture was allowed to warm to room temperature and was then heated at reflux for 16 h. The reaction mixture was allowed to cool to room temperature, poured onto crushed ice, extracted with ether and the combined organic extracts dried over anhydrous potassium carbonate, filtered and concentrated to give a dark yellow oil. Distillation under reduced pressure gave 1-(2-furyl)-3-methylbutanol (11.0 g, 49%) as a colourless oil.

δ_H 7.35 (1H, dd, J 1.8, 0.8 Hz), 6.31 (1H, dd, J 3.1, 1.8 Hz), 6.21 (1H, d, J 2.9 Hz), 4.73 (1H, t, J 6.8 Hz), 2.19 (1H, br s), 1.80-1.64 (3H, m), 0.94 (3H, d, J 6.2 Hz), 0.92 (3H, d, J 6.1 Hz).

(b) N-4-Bromomethylphenylsulphonyl-1-(2-furyl)-3-methylbutylamine

N-4-Bromomethylphenylsulphonyl-1-(2-furyl)-3-methylbutylamine was prepared by the procedures of Example 134 Step (b) and Example 1 Steps (b) and (d) employing 1-(2-furyl)-3-methylbutanol *in lieu* of (4-fluorophenyl)-(2-thienyl)methanol as starting material.

Yellow oil (26% yield for last step after chromatography (1:8 ethyl acetate/hexane)):

δ_H 7.65 (2H, dd, J 6.5, 1.9 Hz), 7.38 (2H, dd, J 8.5, 2.1 Hz), 7.07 (1H, d, J 1.6 Hz), 6.07 (1H, dd, J 3.3, 1.7 Hz), 5.86 (1H, d, J 3.3 Hz), 4.84 (1H, d, J 8.8 Hz), 4.50-4.45 (1H, m), 4.45 (2H, s), 1.69-1.52 (3H, m), 0.88 (3H, d, J 6.4 Hz), 0.87 (3H, d, J 6.3 Hz).

(c) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-furyl)-3-methylbutylamine

N-Methyl-N-4-(1H-2-methylbenzimidazolylmethyl)phenylsulphonyl-1-(2-furyl)-3-methylbutylamine was prepared by the procedure of Example 131 Steps (b) and (c) employing N-4-bromomethylphenylsulphonyl-1-(2-furyl)-3-methylbutylamine *in lieu* of N-4-bromomethylphenylsulphonyl-2-thienylmethylamine.

Pale yellow oil (14.5% yield after chromatography (3-7% methanol in DCM)):

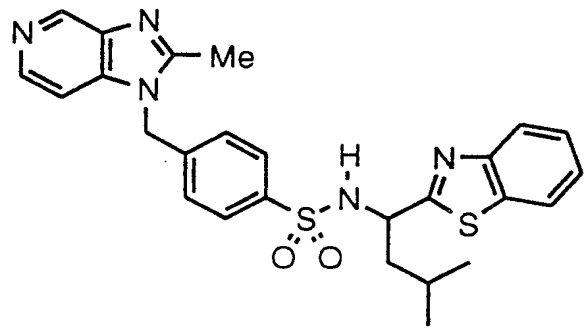
Analysis calculated for $C_{24}H_{28}N_4O_3S$
Requires C 63.69 H 6.24 N 12.38
Found C 63.14 H 6.28 N 12.23

i.r. ($CDCl_3$) 2960, 1610, 1345, 1150, 1015 cm^{-1}

δ_H 8.98 (1H, s), 8.32 (1H, d, J 5.4 Hz), 7.66 (2H, d, J 8.2 Hz), 7.10 (1H, d, J 5.5 Hz), 7.06 (2H, d, J 8.3 Hz), 6.98-6.97 (1H, m), 6.08-6.06 (1H, m), 5.93 (1H, d, J 3.3 Hz), 5.12 (2H, s), 5.10-5.40 (1H, m), 2.55 (3H, s), 2.54 (3H, s), 1.63-1.52 (3H, m), 0.90-0.86 (6H, m);

Example 137

N-4-(1H-2-Methylbenzimidazolylmethyl)phenylsulphonyl-1-(2-benzothiazolyl)-3-methylbutylamine



(a) 1-(2-Benzothiazolyl)-3-methylbutanol

A solution of n-butyllithium (2.5 M in hexanes; 65.1 ml, 0.163 mol) was added to a stirred solution of benzothiazole (20.0 g, 0.148 mol) in dry THF (250 ml) under argon at -78°C. After 10 min a solution of isovaleraldehyde (17.4 ml, 0.163 mol) in dry THF (50 ml) was added slowly and the mixture stirred for 1 h at -78°C. The reaction mixture was removed from the cooling bath and after 10 min was quenched by the addition of excess water and the mixture extracted with ethyl acetate. The combined organic layers were washed with water, dried, filtered and evaporated. Chromatography (20-30% diethyl ether in hexane) gave 1-(2-benzothiazolyl)-3-methylbutanol (5.8 g, 18%) as an amorphous yellow solid.

δ_H 7.99 (1H, dd, J 7.7, 1.0 Hz), 7.90 (1H, dd, J 7.8, 1.1 Hz), 7.48 (1H, ddd, J 8.3, 7.3, 1.2 Hz), 7.38 (1H, ddd, J 8.2, 7.4, 1.1 Hz), 5.16 (1H, dd, J 8.9, 5.1 Hz), 3.00 (1H, br s), 2.01-1.95 (1H, m), 1.89-1.82 (2H, m), 1.04 (3H, d, J 6.4 Hz), 1.03 (3H, d, J 6.5 Hz).

(b) 1-(2-Benzothiazolyl)-3-methylbutylamine

1-(2-Benzothiazolyl)-3-methylbutylamine was prepared by the procedure of Example 134 Step (b) employing 1-(2-benzothiazolyl)-3-methylbutanol *in lieu* of (4-fluorophenyl)-(2-thienyl)methanol as starting material.

Pale yellow oil (98% yield after chromatography (2-4% methanol in DCM)):

δ_H 7.97 (1H, br d, J 8.4 Hz), 7.89 (1H, br d, J 7.7 Hz), 7.72-7.36 (2H, m), 6.66 (2H, br s), 4.43 (1H, dd, J 8.4, 5.4 Hz), 1.88-1.68 (3H, m), 1.01-0.97 (6H, m).

(c) N-4-Bromomethylphenylsulphonyl-1-(2-benzothiazolyl)-3-methylbutylamine

N-4-Bromomethylphenylsulphonyl-1-(2-benzothiazolyl)-3-methylbutylamine was prepared by the procedures of Example 1 Step (b) employing 1-(2-benzothiazolyl)-3-methylbutylamine *in lieu* of L-leucine ethyl ester hydrochloride as starting material.

δ_H 7.88-7.69 (2H, m), 7.72 (2H, d, J 8.4 Hz), 7.44 (1H, ddd, J 8.1, 7.4, 1.2 Hz), 7.37-7.31 (1H, m), 7.19 (2H, d, J 8.1 Hz), 5.58 (1H, d, J 9.0 Hz), 4.85-4.76 (1H, m), 4.27 (2H, s), 1.85-1.72 (3H, m), 0.94 (3H, d, J 6.6 Hz), 0.92 (3H, d, J 6.5 Hz).

(d) N-4-(1H-2-Methylbenzimidazolylmethyl)phenylsulphonyl-1-(2-benzothiazole)-3-methylbutylamine

N-4-(1H-2-Methylbenzimidazolylmethyl)phenylsulphonyl-1-(2-benzothiazolyl)-3-methylbutylamine was prepared by the procedure of Example 131 Step (c) employing N-4-bromomethylphenylsulphonyl-1-(2-benzothiazolyl)-3-methylbutylamine *in lieu* of N-4-bromomethylphenylsulphonyl-2-thienylmethylamine.

Off-white crystalline solid (5% yield after chromatography (4-8% methanol in DCM) and crystallisation (ethyl acetate)): m.p. 195-197°C

Analysis calculated for $C_{24}H_{28}N_4O_3S$
Requires C 63.69 H 6.24 N 12.38
Found C 63.14 H 6.28 N 12.23

i.r. ($CDCl_3$) 2960, 1410, 1345, 1160, 1015 cm^{-1}

δ_H 9.03 (1H, br s), 8.37 (1H, br s), 7.82-7.70 (2H, m), 7.68 (2H, d, J 8.2 Hz), 7.44 (1H, ddd, J 7.7, 7.7, 1.4 Hz), 7.35 (1H, ddd, J 7.6, 7.6, 1.2 Hz), 6.98 (1H, br s), 6.84 (2H, d, J 8.3 Hz), 6.55 (1H, br s), 5.12 (2H, s), 4.83-4.80 (1H, m), 2.37 (3H, s), 1.84-1.70 (3H, m), 0.90 (3H, d, J 5.9 Hz), 0.89 (3H, d, J 5.9 Hz);

δ_C 171.70, 153.57, 152.38, 141.70, 140.52, 140.33, 139.32, 134.60, 128.09, 126.21, 125.30, 122.80, 121.58, 104.50, 54.65, 46.58, 46.22, 24.53, 22.67, 21.59.

Example 138-154

The compounds of Examples 138-154 are prepared by the procedure of Example 136 employing the appropriate organolithium reagent as starting material.

138. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)-3-methylbutylamine

139. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-3-yl)-3-methylbutylamine

140. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(N'-methyl-2-pyrrolyl)-3-methylbutylamine

141. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyrazin-2-yl)-3-methylbutylamine

142. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-methylpyrazin-2-yl)-3-methylbutylamine

143. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-ethylpyrazin-2-yl)-3-methylbutylamine

144. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-ethyl-1,2-pyridazin-3-yl)-3-methylbutylamine

145. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-ethyl-1,3-pyrimidin-5-yl)-3-methylbutylamine

146. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(1,3-dithian-2-yl)-3-methylbutylamine

147. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)pentylamine

148. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(4-fluorophenyl)-1-(2-furyl)methylamine

149. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-(4-methoxyphenyl)-1-(2-furyl)ethylamine

150. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-2-yl)-3-methylbutylamine

151. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-methoxypyridin-3-yl)-3-methylbutylamine

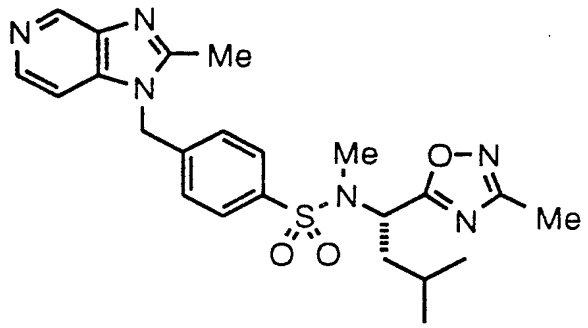
152. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-3-ylmethyl)-3-methylbutylamine

153. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-benzo[b]thienyl)-3-methylbutylamine

154. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(3-methylisoxazol-5-ylmethyl)-3-methylbutylamine

Example 155

N-Methyl-N-4-(1H-2-methylbenzimidazolylmethyl)phenylsulphonyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine



(a) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine amide

Aqueous ammonia (160 ml) was added to a stirred solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester (2.0 g, 4.4 mmol) in methanol (80 ml). The reaction mixture was stirred overnight at room temperature, the solvent removed under reduced pressure and the residue azeotroped with toluene to give crude N-Methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine amide (1.86 g, 99%) as a yellow solid. Chromatography (10% methanol in DCM) followed by crystallisation from acetonitrile gave pure product as a white crystalline solid.

m.p. 198-200°C

Analysis calculated for $C_{21}H_{27}N_5O_3S$
Requires C 58.72 H 6.34 N 16.30
Found C 58.72 H 6.37 N 16.46

i.r. (MeCN) 3470, 3350, 1690, 1180 cm^{-1}

δ_H (CD_3OD) 8.31 (1H, s), 8.27 (1H, d, J 5.7 Hz), 7.78 (2H, d, J 8.4 Hz), 7.74 (1H, d, J 5.8 Hz), 7.27 (2H, d, J 8.4 Hz), 5.61 (2H, s), 4.42 (1H, dd, J 8.9, 6.1

Hz), 2.85 (3H, s), 2.59 (3H, s), 1.55-1.23 (5H, m), 0.82 (3H, d, J 6.2 Hz), 0.80 (3H, d, J 6.2 Hz).

(b) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine

A mixture of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucine amide (1.50 g, 3.5 mmol) in N,N-dimethylacetamide dimethyl acetal (5 ml) was heated at reflux for 2.5 h under argon. The volatiles were removed under reduced pressure and the residue treated with a solution of hydroxylamine hydrochloride (365 mg, 5.25 mmol) in 1M aqueous sodium hydroxide (5.25 ml). Dioxan (5 ml) was added, followed by acetic acid (10 ml) and the resulting solution stirred at room temperature for 0.5 h and then heated at 90°C overnight. The reaction mixure was concentrated, diluted with saturated aqueous potassium carbonate and extracted with DCM, dried and evaporated. Chromatography (6% methanol in DCM) gave N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine as a white foam (215 mg, 13%).

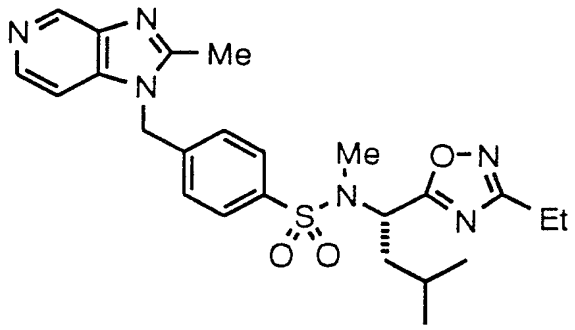
Analysis calculated for $C_{23}H_{32}N_6O_3S.0.7H_2O$
Requires C 58.96 H 6.02 N 17.94
Found C 57.50 H 6.06 N 17.15

i.r. (DCM) 2930, 1610, 1585, 1340, 1150 cm^{-1}

δ_H 9.05 (1H, s), 8.40 (1H, br d), 7.74 (2H, d, J 8.3 Hz), 7.18 (1H, d, J 5.4 Hz), 7.12 (2H, d, J 8.4 Hz), 5.39 (2H, s), 5.39-5.30 (1H, m), 2.81 (3H, s), 2.60 (3H, s), 2.19 (3H, s), 1.84-1.65 (3H, m), 0.99 (3H, d, J 6.1 Hz), 0.97 (3H, d, J 6.2 Hz).

Example 156

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine



(a) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridylmethyl)phenylsulphonyl-L-leucine

A solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridylmethyl)-phenylsulphonyl-L-leucine ethyl ester (6.00 g, 13 mmol) in 8M hydrochloric acid (100 ml) was refluxed for 3 hours. The reaction mixture was concentrated to an orange gum which was taken up in ethyl acetate and evaporated to dryness, to give N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridylmethyl)phenyl-sulphonyl-L-leucine (5.30 g, 94%) as a pale yellow solid.

i.r. (KBr) 3660-3150, 1720-1695, 1610, 1325, 1145 cm^{-1}

δ_H (CD_3OD) 8.36 (1H, s), 8.29 (1H, d, J 5.7 Hz), 7.77 (2H, d, J 8.4 Hz), 7.56 (1H, d, J 5.7 Hz), 7.27 (2H, d, J 8.3 Hz), 5.61 (2H, s), 4.55-4.49 (1H, m), 2.79 (3H, s), 2.59 (3H, s), 1.64-1.46 (3H, m), 0.89 (3H, d, J 6.0 Hz), 0.88 (3H, d, J 5.8 Hz).

(b) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine pentafluorophenyl ester

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine pentafluorophenyl ester was prepared by the procedure of Example 78 Step (a) employing N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucine *in lieu* of 2-(3,4-dimethoxyphenylmercapto)-ethanoate.

δ_H 8.98 (1H, s), 8.31 (1H, d, J 5.8 Hz), 7.78 (2H, d, J 8.3 Hz), 7.23 (1H, d, 5.8 Hz), 7.16 (2H, d, J 8.3 Hz), 5.44 (2H, s), 5.09-5.03 (1H, m), 2.89 (3H, s), 2.58 (3H, s), 1.86-1.65 (3H, m), 1.03 (3H, d, J 5.5 Hz), 1.01 (3H, d, J 5.1 Hz).

(c) N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine

A solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucine pentafluorophenyl ester (1.60 g, 2.7 mmol) in chloroform (50 ml) was treated with propionamide oxime (0.28 g, 3.2 mmol) and heated at reflux for 10 h. The mixture was cooled, washed with saturated aqueous sodium hydrogen carbonate and brine, dried, filtered and concentrated. The residue was dissolved in ethyl acetate and heated at reflux over activated molecular sieves. The reaction mixture was filtered and concentrated. Chromatography (7% methanol in DCM) gave N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine (673 mg, 52 %) as a brown oil. A portion was further purified by reverse phase preparative HPLC (C-18 silica; 50-80% 0.01 M ammonium acetate in methanol) to give N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine as a white solid.

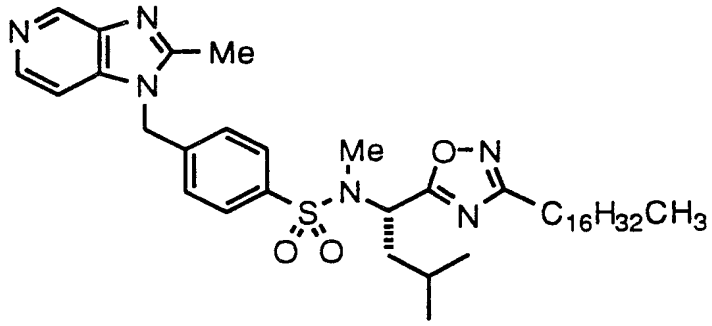
i.r. ($CDCl_3$) 2965, 1615, 1585, 1345, 1165 cm^{-1}

δ_H 9.00 (1H, s) 8.35 (1H, d, J 5.6 Hz), 7.67 (2H, d, J 8.3 Hz), 7.12 (1H, d, J 5.4 Hz), 7.06 (2H, d, J 8.3 Hz), 5.38-5.32 (1H, m), 5.34 (2H, s), 2.78 (3H, s), 2.55 (3H, s), 2.50 (2H, q, J 7.5 Hz), 2.13-1.62 (3H, m), 1.11 (3H, t, J 7.6 Hz), 0.95 (3H, d, J 5.9 Hz), 0.94 (3H, d, J 6.2 Hz);

δ_C 176.58, 171.19, 153.19, 142.17, 142.05, 140.14, 139.98, 139.84, 138.79, 128.18, 126.58, 104.52, 51.58, 46.72, 39.56, 29.54, 24.22, 22.63, 21.35, 19.37, 13.82, 11.07.

Example 157

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-heptadecyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine



N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-heptadecyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine was prepared by the procedure of Example 156 employing octadecylamide oxime *in lieu* of propionamide oxime.

Pale brown oil (21% yield after chromatography (5-8.5% methanol in DCM)):

i.r. ($CDCl_3$) 2930, 1585, 1350, 1155 cm^{-1}

δ_H 9.00 (1H, s), 8.35 (1H, d, J 4.9 Hz), 7.68 (2H, d, J 8.4 Hz), 7.12 (1H, d, J 5.5 Hz), 7.07 (2H, d, J 8.4 Hz), 5.38-5.31 (3H, m), 2.77 (3H, s), 2.55 (3H, s), 2.49 (2H, dd, J 7.9, 7.3 Hz), 1.81-1.52 (5H, m), 1.36-1.17 (32H, m), 0.96 (3H, d, J 6.1 Hz), 0.94 (3H, d, J 6.3 Hz), 0.85 (3H, t, J 6.6 Hz);

δ_C 176.49, 170.32, 153.29, 142.11, 141.95, 140.17, 139.95, 139.86, 138.73, 128.18, 126.59, 104.59, 51.52, 46.73, 39.51, 31.80, 29.57, 29.36, 29.23, 29.07, 28.95, 26.76, 25.66, 24.22, 22.66, 22.56, 21.37, 13.99, 13.86.

Examples 158-161

The compounds of Example 158-161 are prepared by the procedure of Example 156 employing the appropriate amide oxime *in lieu* of propionamide oxime.

158. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(3-propyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine

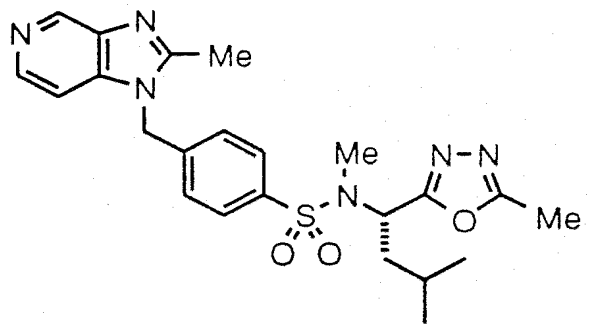
159. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(3-n-butyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine

160. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine

161. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-benzyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine

Example 162

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine



Excess hydrazine hydrate (1.7 ml) was added to a solution of N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucine ethyl ester (2.00 g, 4.4 mmol) in toluene (3 ml) and the mixture heated at reflux for 7 days. The mixture was cooled and triethylorthoacetate (10 ml) was added and the resulting mixture heated at reflux overnight. The volatiles were removed under reduced pressure and the residue partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic layer was separated and washed with brine, dried, filtered and evaporated. The residue was filtered through a pad of silica (eluting with 6% methanol in DCM) to give a pale pink oil, which was then heated at ca. 160°C for 24 h under argon. Chromatography (5% methanol in DCM) gave N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-methyl-butylamine (257 mg, 13%) as a yellow oil.

i.r. (DCM) 1610, 1590, 1340, 1150 cm^{-1}

δ_H 8.94 (1H, s), 8.29 (1H, d, J 5.4 Hz), 7.64 (2H, d, J 8.4 Hz), 7.09 (1H, d, J 5.6 Hz), 7.04 (2H, d, J 8.3 Hz), 5.32 (2H, s), 5.29-5.23 (1H, m), 2.69 (3H, s), 2.51 (3H, s), 2.22 (3H, s), 1.70-1.64 (2H, m), 1.59-1.49 (1H, m), 0.87 (3H, d, J 6.3 Hz), 0.85 (3H, d, J 6.5 Hz);

δ_C 164.21, 163.55, 153.26, 141.69, 141.65, 139.98, 139.60, 138.55, 104.56, 53.30, 50.58, 46.54, 38.78, 29.29, 24.04, 22.44, 21.37, 13.77, 10.51.

Examples 163-165

The compounds of Example 163-165 are prepared by the procedure of Example 162 employing the appropriate trialkylortho ester deivative *in lieu* of triethylorthoacetate.

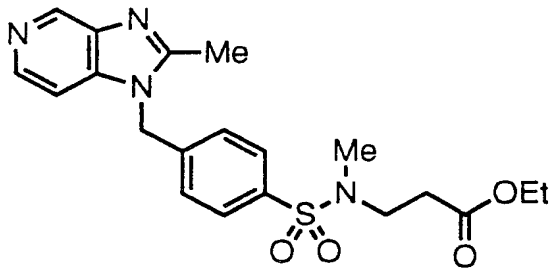
163. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(5-ethyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine

164. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(5-propyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine

165. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine

Example 166

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-β-alanine ethyl ester



N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-β-alanine ethyl ester was prepared by the procedures of Example 1 Steps (b) and (d) and Example 131 Step (c) employing β-alanine ethyl ester hydrochloride as starting material.

Colourless oil (10% yield for last step after chromatography (5% methanol in DCM)):

i.r. ($CDCl_3$) 1725, 1340, 1160 cm^{-1}

δ_H 8.93 (1H, br s), 8.27 (1H, d, J 5.5 Hz), 7.63 (2H, d, J 8.3 Hz), 7.14-7.06 (3H, m), 5.34 (2H, s), 4.02 (2H, q, J 7.1 Hz), 3.21 (2H, t, J 7.2 Hz), 2.67 (3H, s), 2.51 (3H, s), 2.50 (2H, t, J 7.1 Hz), 1.15 (3H, t, J 7.2 Hz);

δ_C 170.81, 153.32, 141.62, 141.58, 140.05, 139.89, 137.40, 132.15, 128.30, 127.96, 126.77, 104.61, 60.60, 46.55, 45.88, 35.28, 33.49, 13.90.

Examples 167-172

The compounds of Example 167-172 are prepared by the procedure of Example 166 employing the appropriate amino acid derivative *in lieu* of β-alanine ethyl ester hydrochloride

167. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-3-amino-5-methylhexanoic acid ethyl ester

168. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-3-amino-5-methylhexanoic acid isopropyl ester

169. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-3-amino-5-methylhexanoic acid n-butyl ester

170. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-3-amino-5-methylhexanoic acid benzyl ester

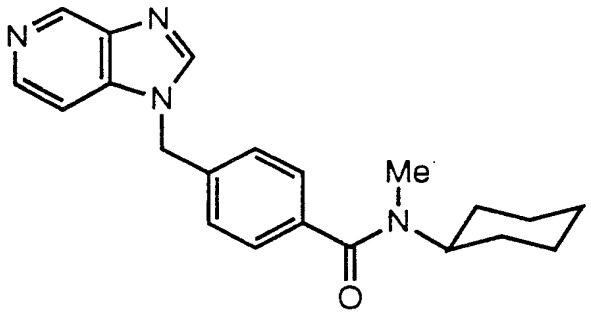
171. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-3-amino-4-phenylbutanoic acid ethyl ester

172. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-3-amino-4-(4-methoxyphenyl)butanoic acid ethyl ester

COMPARATIVE EXAMPLE

N-Cyclohexyl-N-methyl-4-(1H-imidazo[4,5-c]pyridinylmethyl)benzamide

This compound is not within the scope of the invention: It has been included here as a comparative example. This compound was described in EP-A-0260613.



Comparative Example

(a) N-Cyclohexyl-N-methyl-4-methylbenzamide

To an ice cold stirred solution of N-methylcylohexylamine (20 ml, 0.15 mol) and triethylamine (22 ml) in dry THF (100 ml) under argon was slowly added p-toluoyl chloride (20 ml, 0.15 mol). A white precipitate formed. The ice bath was removed and the mixture stirred at ambient temperature for 24 h. Ice cold 2M hydrochloric acid (100 ml) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3x100 ml). The combined organics were washed with brine (3x100 ml), dried, filtered and evaporated to give the crude amide, which was crystallised from hexane to give N-cyclohexyl-N-methyl-4-methylbenzamide (30.9 g, 87%) as a white crystalline solid.

m.p. 70-71°C

i.r. (nujol) 2920, 1640 cm^{-1}

δ_H 7.26 (2H, d, J 8.0 Hz), 7.18 (2H, d, J 8.3 Hz), 4.50, 3.50 (1H, 2br m), 3.08-2.68 (3H, br m), 2.37 (3H, s), 1.93-0.93 (10H, br m).

(b) N-Cyclohexyl-N-methyl-4-bromomethylbenzamide

Utilising the procedure described in Example 1 Step (a) employing N-cyclohexyl-N-methyl-4-methylbenzamide *in lieu* of p-toluene-sulphonyl chloride and tetrachloromethane as solvent yielded crude N-cyclohexyl-N-methyl-4-bromomethylbenzamide (67%) as an orange waxy solid.

i.r. (CH_2Cl_2) 2935, 1720 cm^{-1}

δ_H 7.46 (2H, d, J 8.1 Hz), 7.34 (2H, d, J 8.1 Hz), 4.51 (2H, s), 3.78, 3.50 (1H, 2br m), 2.97 (3H, br s), 1.89-0.98 (10H, br m).

(c) N-Cyclohexyl-N-methyl-4-(1H-imidazo[4,5-c]pyridinylmethyl)-benzamide

Sodium bis(trimethylsilyl)amide (22 ml of 1 M solution in THF) was added to a stirred solution of imidazo[4,5-c]pyridine (2.60 g, 0.02 mol) in dry THF (200 ml) under argon. A fine white precipitate formed. After 90 m the mixture was treated with N-cyclohexyl-N-methyl-4-bromomethylbenzamide (6.20 g, 0.02 mol) dissolved in dry THF (50 ml). The mixture was allowed to warm to ambient temperature and stirred overnight. Methanol (1 ml) was added, followed by water and the product extracted using ethyl acetate (3 x 150 ml). The combined organic layers were washed with water (2 x 100 ml), dried over anhydrous potassium carbonate and the solvent removed to give the crude product. Chromatography (10% methanol in ethyl acetate) followed by repeated fractional crystallisation (6 times from ethyl acetate/DIPE) gave the desired regioisomer N-cyclohexyl-N-methyl-4-(1H-imidazo[4,5-c]pyridinylmethyl)-benzamide (0.39 g, 5%) as an off white crystalline solid.

m.p. 121-123°C

Analysis calculated for $C_{21}H_{24}N_4O.0.6H_2O$
Requires C 70.21 H 7.07 N 15.60
Found C 70.08 H 6.91 N 15.37

i.r. (KBr) 3080, 2930, 1615 cm^{-1}

δ_H 9.17 (1H, s), 8.42 (1H, d, J 5.6 Hz), 8.03 (1H, s), 7.37 (2H, d, J 7.8 Hz), 7.27-7.19 (3H, m), 5.42 (2H, s), 4.50, 3.37 (1H, 2br m), 2.96, 2.76 (3H, 2br s), 2.05-1.02 (10H, br m).

PHARMACOLOGY EXAMPLE 1

The inhibition of [^{3}H]-PAF binding to human platelet plasma membrane by compounds of general formula I was determined by isotopic labelling and filtration techniques. Platelet concentrates were obtained from a hospital blood bank. These platelet concentrates (500-2500 ml.) were centrifuged at 800 rpm for 10 minutes in a SORVALL RC3B centrifuge to remove the red blood cells present. (The word SORVALL is a trade mark.) The supernatant was subsequently centrifuged at 3,000 rpm in a SORVALL RC3B centrifuge to pellet the platelets present. The platelet rich pellets were resuspended in a minimum volume of buffer (150 mM NaCl, 10 mM Tris, 2 mM EDTA, pH 7.5) and layered onto Ficoll-Paque gradients, 9 ml platelet concentrate to 2 ml Ficoll, and centrifuged at 1,900 rpm for 15 minutes in a SORVALL RT6000 centrifuge. This step removes the residual red blood cells and other nonspecific material such as lymphocytes from the preparation. The platelets which form a band between the plasma and the Ficoll were removed, resuspended in the above buffer and centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge. The pelleted platelets were resuspended in buffer (10 mM Tris, 5mM $MgCl_2$, 2 mM EDTA, pH 7.0), snap freezed in liquid N_2 and allowed to thaw slowly at room temperature in order to lyse the platelets. The latter step was repeated at least 3 times to ensure proper lysis. The lysed platelets were centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge and resuspended in buffer. The latter step was repeated twice in order to remove any cytoplasmic proteins which may hydrolyse the platelet activating factor (PAF) receptor. The prepared platelet membranes may be stored at -70°C. After thawing the prepared membranes were centrifuged in a SORVALL RT6000 at 3,000 rpm for 10 minutes and resuspended in assay buffer.

The assay was conducted by preparing a series of Tris-buffered solutions of the selected antagonist of predetermined concentrations. Each of these solutions contained [^{3}H]-PAF (0.5 nM; 1-*O*-[^{3}H]octadecyl-2-acetyl-*sn*-glycero-3-phosphoryl choline with a specific activity of 132 Ci/mmol), unlabelled PAF (1000 nM), a known amount of the test antagonist, and a sufficient amount of Tris-buffer solution (10mM Tris, 5mM $MgCl_2$, pH 7.0, 0.25% BSA) to make the final volume 1ml. Incubation was initiated by the addition of 100 µg of the isolated membrane fraction to each of the above solutions at 0°C. Two control samples, one (C1) which contained all the ingredients described above except the antagonist and the other (C2) contains C1 plus a 1000-fold excess of unlabelled PAF, were also prepared and incubated simultaneously with the test samples.

After 1 hour incubation, each solution was filtered rapidly under *vacuo* through a WHATMAN GF/C glass fibre filter in order to separate unbound PAF from bound PAF. (The word WHATMAN is a trade mark.) The residue in each case was rapidly washed 4 times with 5 ml cold (4°C) Tris-buffer solution. Each washed residue was dried under vacuum on a sampling manifold and placed into vials containing 20 ml of OPTIPHASE MP scintillation fluid and the radioactivity counted in a liquid scintillation counter. (The word OPTIPHASE is a trade mark.) Defining the counts for total binding with antagonist from a test sample as "TBA"; the counts for total binding from the control sample C1 as "TB"; and the counts for nonspecific binding from the control sample C2 as "NSB", the percent inhibition of each test antagonist can be determined by the following equation:

%Inhibition = [(TB-TBA)/SB]x100

where the specific binding SB = TB-NSB

Table 1 lists results from this assay for inhibition of [^{3}H]-PAF receptor binding for illustrative examples of the compounds of this invention. Also presented in Table 1 is the result for a comparative example (N-cyclohexyl-N-methyl-4-(1H-imidazo[4,5-c]pyridinylmethyl)benzamide. This compound (a PAF antagonist described in EP-A-0260613) is not within the scope of the invention.

Table 1: Results for inhibition of [^{3}H]-PAF receptor binding

Example	Inhibition of [^{3}H]-PAF binding IC_{50} nM
1	7
44	1
45	0.5
47	2
49	2
79	4
109	3
155	2
Comparative Example	10,000

PHARMACOLOGY EXAMPLE 2

The activity of the compounds of general formula I is also demonstrated *in vivo* by their ability to reverse the hypotension caused by an infusion of PAF in rats. Male Sprague-Dawley rats (300-350 g) were anaesthetised with a mixture of sodium pentobarbitone, 22.5 mg/kg and thiopental 62.5 mg/kg. Through a midline incision in the neck, the trachea was cannulated and the animals breathed spontaneously. A carotid artery was cannulated for the measurement of blood pressure and this signal was used to trigger a rate meter to measure heart rate. Both jugular veins were cannulated: one for the infusion of PAF and the other for the bolus administration of test compounds.

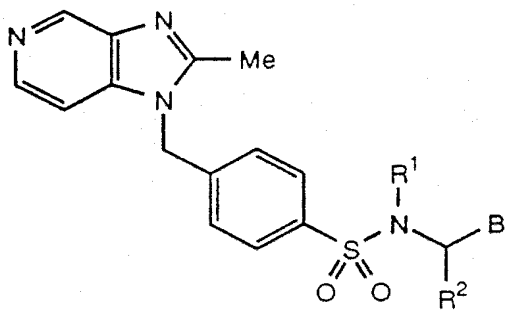
PAF, 100 ng/kg/min was infused *i.v.* until a sustained fall in mean blood pressure of 50 mmHg was achieved. Test compounds were administered *i.v.* as a bolus and resulted in a dose dependent reversal of the PAF induced hypotension. The peak of this reversal was measured and the dose to cause a 50% reversal of the hypotensive PAF response (ED_{50}) calculated by straight line interpolation and the results are presented in Table 2.

Table 2: Results for inhibition of PAF-induced hypotension in the rat

Example	ED_{50} (μg/kg *i.v.*)
44	4.6
49	2.2
78	5.8
108	6.6
156	0.6
Comparative Example	150

CLAIMS

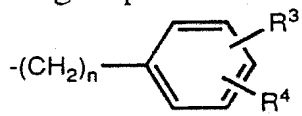
1. A compound of general formula I;



I

wherein:

R^1 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(COC_1-C_6 alkyl)phenyl, -(CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D represents a group:



wherein n is an integer from 0 to 3, and each of R^3 and R^4 is independently hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, halogen, -CN, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CONH(C_1$-C_6 alkyl)2, -CHO, -CH_2OH, -CF_3, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2 or -NHCOMe;

R^2 represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)2, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

B represents a) a -$(CH_2)_mX$ group wherein m is an integer from 0 to 2 and the group X represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen, -C_1-C_4 perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, -$CONH_2$, a group -D wherein D is as defined above, -R^5, -OR^5, -SR^5, -SOR^5, -SO_2R^5, -NHR^5, -NR^5R^5, -CO_2R^5 or -$CONHR^5$ wherein R^5 is -C_1-C_{18} alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl or -C_4-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, -C_1-C_4 perfluoroalkyl, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group:

b) a group Y, wherein Y is -CH_2OH, -$CH_2OC(=O)R^6$, -$CH_2OC(=O)C(=O)OR^6$, -$CH_2OSO_2R^6$, -$CH_2OP(=O)OR^6OR^6$, -$NHC(C=O)OR^6$, -$CH_2OC(=O)NHR^6$, -$CH_2CO_2R^6$ or -$CH_2OC(=O)CH_2SR^6$ group wherein R^6 is, -C_1-C_{18} alkyl, -C_2-C_{20} alkenyl, -C_2-C_{18} alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, a group D as defined above or a group -$(CH_2)_mX$ as defined above;

c) a -$CH_2OC(=O)CHR^2Y$ group wherein R^2 and Y are as defined above;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

2. A compound as claimed in Claim 1, in which R^1 represents a hydrogen atom, a -C_1-C_6 alkyl group, a -C_2-C_6 alkenyl group or a group -D.

3. A compound as claimed in Claims 1 or Claim 2, in which R^2 represents a hydrogen atom, a -C_1-C_6 alkyl group, a -C_2-C_6 alkenyl group, a -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl group, a side chain of a naturally occurring amino acid or a group D.

4. A compound as claimed in any one of Claims 1 to 3, containing a group D wherein R^3 represents a hydrogen atom, a -C_1-C_6 alkyl group, a halogen atom, a -CF_3 group or a -OC_1-C_6 alkyl group, and R^4 represents a hydrogen atom or a -OC_1-C_6 alkyl group.

5. A compound as claimed in any one of Claims 1 to 4, wherein B is a group -$(CH_2)_m$X wherein m is as defined in Claim 1 and X represents a furanyl group, a thienyl group, a pyrrolinyl group, a tetrahydrofuranyl group, an oxadiazolyl group, a thiadiazolyl group, a pyridinyl group, a piperazinyl group, a benzotriazolyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a dithianyl group, a benzo[b]thienyl group, a isoxazolyl group or a quinolinyl group.

6. A compound as claimed in Claim 5, wherein the group X is substituted with one or more substituents selected from hydrogen, a group -D, -R^5 or -CO_2R^5, wherein D and R^5 are as defined in Claim 1.

7. A compound as claimed in Claim 6, wherein R^5 represents a -C_1-C_{18} alkyl group or a -OC_1-C_6 alkyl group.

8. A compound as claimed in any one of Claims 1 to 4, wherein B is a group Y as defined in Claim 1 wherein R^6 represents a -C_1-C_{18} alkyl group, a -C_2-C_{20} alkenyl group, a group -D or a group -$(CH_2)_m$X as defined in Claim 1 or in any one of Claims 5 to 7

9. A compound as claimed in Claim 1, wherein R^1 is hydrogen or methyl, R^2 is sec-butyl (side chain of L-leucine) and B is a group -$(CH_2)_m$X as defined in Claim 1 or a group Y wherein Y is a -CH_2OH, -$CH_2OC(=O)R^6$, -$CH_2OC(=O)NHR^6$ or -$CH_2OC(=O)CH_2SR^6$ group.

10. N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D-leucinol,
N-Ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
N-Allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,

N-Propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
N-Benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
N-4-Methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-isoleucinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylalaninol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-valinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-tryptophanol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-methioninol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-O-methyl-L-tyrosinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-norleucinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylglycinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylglycinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-ethylglycinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-allylglycinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopropylalaninol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopentylalaninol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclohexylalaninol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D-leucinol,

O-Ethanoyl-N-ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Ethanoyl-N-allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Ethanoyl-N-propyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Ethanoyl-N-benzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Ethanoyl-N-4-methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-isoleucinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylalininol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-valinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-tryptophanol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-methioninol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-O'-methyl-L-tyrosinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-norleucinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-phenylglycinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-t-butylglycinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-ethylglycinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-D,L-allylglycinol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopropylalininol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclopentylalininol,
O-Ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-cyclohexylalininol,

O-Octadecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-2-Furoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-Ethyloxaloyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-Benzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-2-Acetoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Propanoyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-Propanoyl-N-ethyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-Propanoyl-N-allyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-Propanoyl-N-methoxybenzyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-isoleucinol,
O-Propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-cyclopentylalininol,
O-Butanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-Pentanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-Hexanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-Octanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-Decanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-Dodecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-Tetradecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,

O-Hexadecanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-2-Thiophenecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-2-Tetrahydrofuroyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-2-Pyridinecarbonyl-N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-3-Pyridinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-4-Pyridinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-3-Quinolinecarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-2-Trifluoromethylbenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-2-Bromobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-3-Chlorobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-4-Methoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-4-Fluorobenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-3,4-Dimethoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-3-Chloro-4-methoxybenzoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-2,2-Dimethylpropanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-2-(3,4-Dimethoxyphenylmercapto)ethanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Retinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl-L-leucinol,
O-2-(4-Methoxyphenyl)ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-2-(3,4-Dimethoxyphenyl)ethanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,

O-3-(4-Methoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-3-(3,4-Dimethoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-3-(3-Chloro-4-methoxyphenyl)propanoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-3-(Pyridin-3-yl)propanoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
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O-(N',N'-Dibenzyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-(N'-Benzyloxycarbonyl)glycinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-(N'-Benzyloxycarbonyl)-D-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-(N'-Benzyloxycarbonyl)-L-phenylalininoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-(N',N'-dibenzyl)glycinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
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O-(N'-Butoxycarbonyl)-L-leucinoyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-(N'-Benzyloxycarbonyl)-L-valinoyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-(N'-Benzyloxycarbonyl)-L-phenylglycinoyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Diethoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Dimethoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Diphenoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Diisopropoxyphosphoryl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Methylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,

O-Ethylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl-L-leucinol,
O-Propylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Phenylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-4-Methylphenylsulphonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Benzylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)-L-leucinol,
O-4-Ethoxycarbonylpiperazinecarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-5-Ethyl-1,3,4-thiadiazol-2-ylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Pyridin-2-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Octadecylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Methylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Ethylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-n-Propylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-i-Propylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-n-Pentylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-n-Hexylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-n-Octylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-n-Decylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-n-Dodecylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-n-Tetradecylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,

O-n-Hexadecylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-t-Butylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl-L-leucinol,
O-Pyridin-2-ylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Pyridin-4-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-Pyridin-3-ylmethylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-4-Methoxyphenylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-3,4-Dimethoxybenzylaminocarbonyl-N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-2-(4-Methoxyphenyl)ethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-2-(3,4-Dimethoxyphenyl)ethylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-3-(3,4-Dimethoxyphenyl)propylaminocarbonyl-N-methyl-N-4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
O-3-(Pyridin-3-yl)propylaminocarbonyl-(N-methyl-N-4-(1H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl-L-leucinol,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-thienylmethylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-tetrahydrofurfurylamine,
N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-(N'-methylpyrrol-2-yl)ethylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(4-fluorophenyl)-1-(2-thienyl)methylamine,
N-4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)propylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-furyl)-3-methylbutylamine,
N-4-(1H-2-Methylbenzimidazolylmethyl)phenylsulphonyl-1-(2-benzothiazolyl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)-3-methylbutylamine,

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-3-yl)-3-methylbutylamine,
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N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyrazin-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-methylpyrazin-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-ethylpyrazin-2-yl)-3-methylbutylamine
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(6-ethyl-1,2-pyridazin-3-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-ethyl-1,3-pyrimidin-5-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(1,3-dithian-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-thienyl)pentylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(4-fluorophenyl)-1-(2-furyl)methylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-2-(4-methoxyphenyl)-1-(2-furyl)ethylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-methoxypyridin-3-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(pyridin-3-ylmethyl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(2-benzo[b]thienyl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-methylisoxazol-5-ylmethyl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylbenzimidazolylmethyl)phenylsulphonyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-heptadecyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,

N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-propyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-n-butyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(3-benzyl-1,2,4-oxadiazol-5-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-ethyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-propyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-3-methylbutylamine,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-β-alanine ethyl ester,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid ethyl ester,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid isopropyl ester,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid n-butyl ester,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-5-methylhexanoic acid benzyl ester,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-4-phenylbutanoic acid ethyl ester,
N-Methyl-N-4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl-3-amino-4-(4-methoxyphenyl)butanoic acid ethyl ester,

or a salt of such a compound.

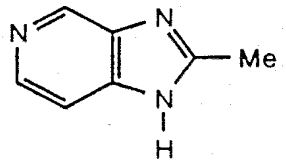
11. A compound as claimed in any one of Claims 1 to 10 for use in human or veterinary medicine, particularly in the management of diseases or conditions mediated by platelet activating factor.

12. The use of a compound as claimed in any one of Claims 1 to 10 in the preparation of an agent for the treatment or prophylaxis of diseases or conditions mediated by platelet activating factor.

13. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of Claims 1 to 10 and a pharmaceutically and/or veterinarily acceptable carrier.

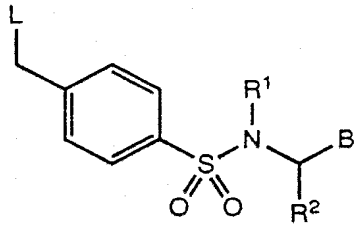
14. A process for preparing a compound of general formula I as defined in Claim 1, the process comprising:

(a) treating an imidazole derivative represented by formula II



II

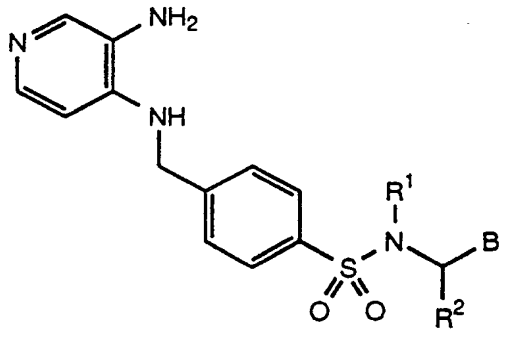
with a suitable base (e.g. sodium hydride, potassium hydride, sodium bis(trimethylsilyl)amide, or potassium hydroxide), followed by a compound of general formula III



III

wherein R^1, R^2 and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

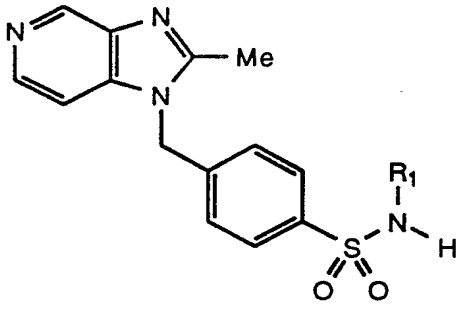
(b) treating a substituted diamino compound of general formula IV



IV

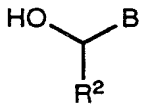
wherein R^1, R^2 and B are as defined in general formula I, with acetic acid or a suitable derivative thereof; or

(c) treating a sulphonamide of general formula V



V

wherein R^1 is as defined in general formula I, with an alcohol of general formula VI

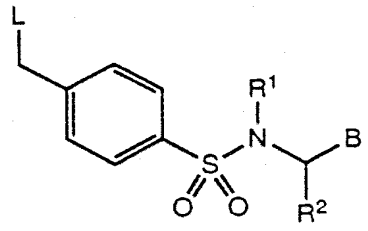


VI

wherein R^2 and B are as defined in general formula; and

(d) optionally after step (a), step (b) or step (c) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

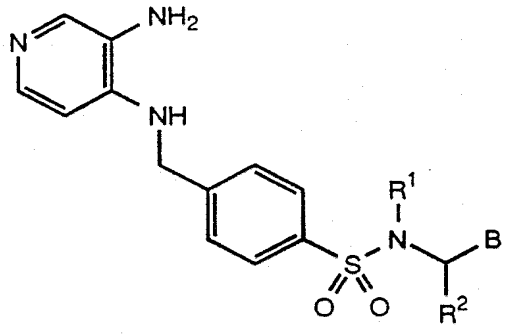
15. A compound of general formula III



III

wherein R^1, R^2 and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy.

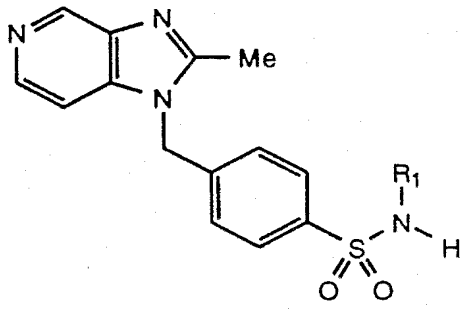
16. A substituted diamino compound of general formula IV



IV

wherein R^1, R^2 and B are as defined in general formula I.

17. A sulphonamide of general formula V



V

wherein R^1 is as defined in general formula I.

18. A method for the treatment or prophylaxis of diseases or physiological conditions of humans or mamalian animals mediated by platelet activating factor, comprising administering to the patient an amount of a compound as claimed in

any of claims 1 to 10 effective to antagonise the effects of platelet activating factor on target cells responsible for such diseases or physiological conditions.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00273

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D471/04; A61K31/435; C07F9/6561; A61K31/66
C07D213/74; C07D333/20; C07C311/17; C07D307/14 ./.

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; C07F ; C07C ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 260 613 (SEARLE) 23 March 1988 see claims 1,86	1,11
P,A	WO,A,9 203 423 (BRITISH BIO-TECHNOLOGY) 5 March 1992 see claims 1,22	1,11

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 MAY 1993	- 8. 06. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00273

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C07D207/32; C07D307/52; C07D277/64; //(C07D471/04, 235:00,221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]

[10] Special categories of cited documents:

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300273
SA 69878

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0260613	23-03-88	US-A- 4804658	14-02-89
		AU-B- 601484	13-09-90
		AU-A- 7829287	17-03-88
		JP-A- 63088182	19-04-88
		US-A- 4962106	09-10-90
WO-A-9203423	05-03-92	AU-A- 8421691	17-03-92
		AU-A- 8426891	17-03-92
		WO-A- 9203422	05-03-92
		US-A- 5200412	06-04-93
		US-A- 5180723	19-01-93

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(51) International Patent Classification 5 :
C07C 65/21, A61K 31/085, 31/19, 31/235, C07C 69/76, 205/35, 205/57, 311/02, 311/51, 235/42, 235/34, 217/58, 217/80, 219/14, 255/54, 271/02, 259/10, C07D 213/79, 239/10, 401/14, 401/06, 207/26, 311/22, 279/16, 237/14, 471/04, 235/06, 333/38, 257/04, 209/42, 277/32, 277/22, 277/64, 513/04, 498/04, 285/12, 233/60, 231/12, 235/18, 233/90, A61K 31/16, 31/325, 31/275, 31/135, 31/35, 31/38, 31/395 // (C07D 471/04, 235:00, 221:00) (C07D 513/04, 277:00, 221:00) (C07D 498/04, 263:00, 221:00)

A1

(11) International Publication Number: WO 94/12461

(43) International Publication Date: 9 June 1994 (09.06.94)

(21) International Application Number: PCT/US93/10228

(22) International Filing Date: 29 October 1993 (29.10.93)

(30) Priority Data:
07/984,408 2 December 1992 (02.12.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US 07/984,408 (CIP)
Filed on 2 December 1992 (02.12.92)

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(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

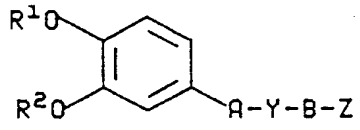
(81) Designated States: AU, BR, CA, CZ, JP, KR, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CATECHOL DIETHERS AS SELECTIVE PDE_{IV} INHIBITORS

(57) Abstract

This invention relates to 4-substituted catechol diether compounds which are selective inhibitors of phosphodiesterase (PDE) type IV. The compounds of the present invention are useful in inhibiting PDE_{IV} and in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases. This invention also relates to pharmaceutical compositions comprising the compounds hereof.



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CATECHOL DIETHERS AS SELECTIVE PDE_{IV} INHIBITORS

Background of the Invention

This invention relates to a series of 4-substituted catechol diether compounds which are selective inhibitors of phosphodiesterase (PDE) type IV and as such are useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases.

This invention also relates to the pharmaceutically acceptable salts of said compounds; to a method of using such compounds in the treatment of inflammatory conditions in mammals, especially humans; and to pharmaceutical compositions useful therefor.

The "inflammatory conditions" which can be treated according to this invention include, but are not limited to, chronic obstructive pulmonary disease, shock, atopic dermatitis, bronchitis, rheumatoid arthritis and osteoarthritis.

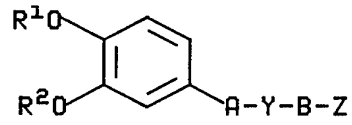
Since the recognition that cyclic AMP is an intracellular second messenger (E. W. Sutherland, and T. W. Rall, Pharmacol. Rev., 1960, 12, 265), inhibition of the phosphodiesterases have been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J. A. Beavo and D. H. Reifsnyder, TiPS, 1990, 11, 150), and their selective inhibition has led to improved drug therapy (C. D. Nicholson, R. A. Challiss and M. Shahid, TiPS, 1991, 12, 19). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M. W. Verghese *et al.*, J. Mol. Cell Cardiol., 1989, 12 (Suppl. II), S 61) and airway smooth muscle relaxation (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donnell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing cardiovascular effects or antiplatelet effects.

Certain pyrimidone compounds have been disclosed to be useful as antidepressants by Saccomano et al., in European Patent Application EPO 247 725 A2. The same pyrimidone compounds have been disclosed to be useful against asthma and certain skin disorders in International Patent Application No. PCT/US90/02162, filed April 20, 1990.

Summary of the Invention

This invention is concerned with a series of 4-substituted catechol diether compounds and to the pharmaceutically acceptable salts of such compounds. These new compounds possess antiinflammatory activity in mammals, especially humans.

The compounds of the present invention are of the formula (I)



(I)

the racemic-diastereomeric mixtures and optical isomers of compounds of formula I and the pharmaceutically acceptable salts thereof wherein

R^1 is selected from the group consisting of methyl, ethyl, difluoromethyl and trifluoromethyl;

R^2 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, alkoxyalkl having 3 to 7 carbons in the alkoxy portion and 2 to 4 carbons in the alkyl portion, phenoxyalkyl having 2 to 6 carbons in the alkyl portion, $(C_3\text{-}C_7)$cycloalkyl, $(C_6\text{-}C_9)$polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion, phenylaminoalkyl having 2 to 6 carbons in the alkyl portion and the amino may be optionally substituted with $(C_1\text{-}C_4)$ alkyl and indanyl,

where the alkyl portion of said alkyl, phenoxyalkyl, cycloalkyl, polycycloalkyl, phenylalkyl and indanyl may optionally be substituted with one or more fluorine atoms, -OH or $(C_1\text{-}C_4)$alkoxy,

and the aryl portion of said phenylalkyl, phenoxyalkyl and indanyl may optionally be substituted with $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or halogen;

A and B are independently selected from the group consisting of a covalent bond, optionally substituted $(C_1\text{-}C_5)$alkylene, optionally substituted $(C_2\text{-}C_5)$alkenyl and optionally substituted phenylene,

where said optionally substituted alkylene may be monosubstituted and each substituent is selected from the group consisting of oxo, $(C_1\text{-}C_4)$alkoxy, CO_2R^6 and hydroxy,

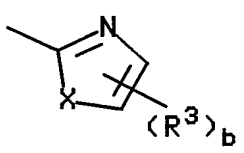
said optionally substituted alkenyl may be monosubstituted with $(C_1\text{-}C_4)$alkoxy or CO_2R^6, and

said optionally substituted phenylene may be monosubstituted with (C_1-C_4)alkoxy, CO_2R^6 or hydroxy,

wherein R^6 is hydrogen or (C_1-C_4)alkyl;

Y is selected from the group consisting of a covalent bond, O, NR^6 and S wherein R^6 is as defined above;

Z is selected from the group consisting of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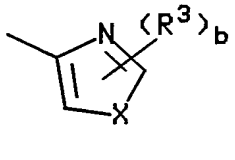
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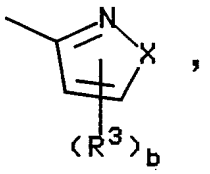
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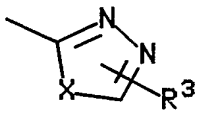
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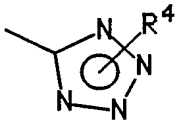
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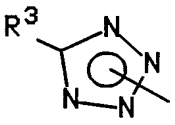
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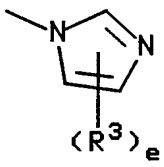
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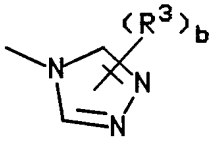
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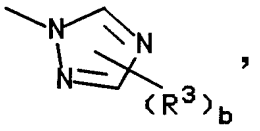
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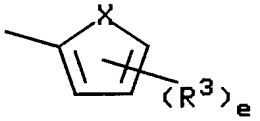
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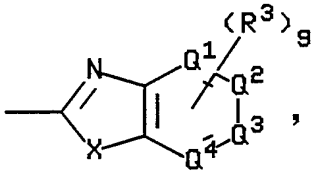
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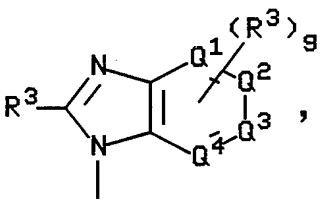
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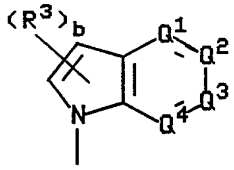
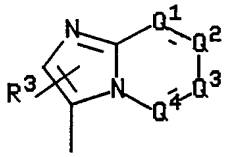
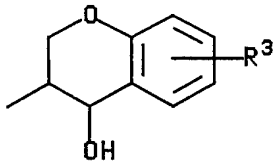

(R3)b
Q1
Q2
Q3
Q4
N

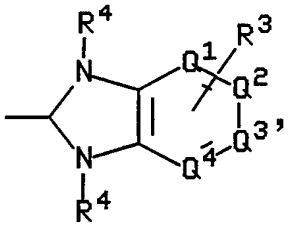
,


N
Q1
Q2
R3
N
Q3
Q4

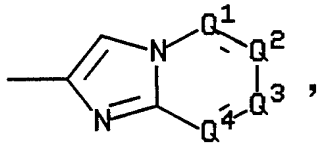
,


O
R3
OH

,


R4
N
Q1
R3
Q2
Q3
Q4
N
R4

,


Q1
N
Q2
Q3
N
Q4

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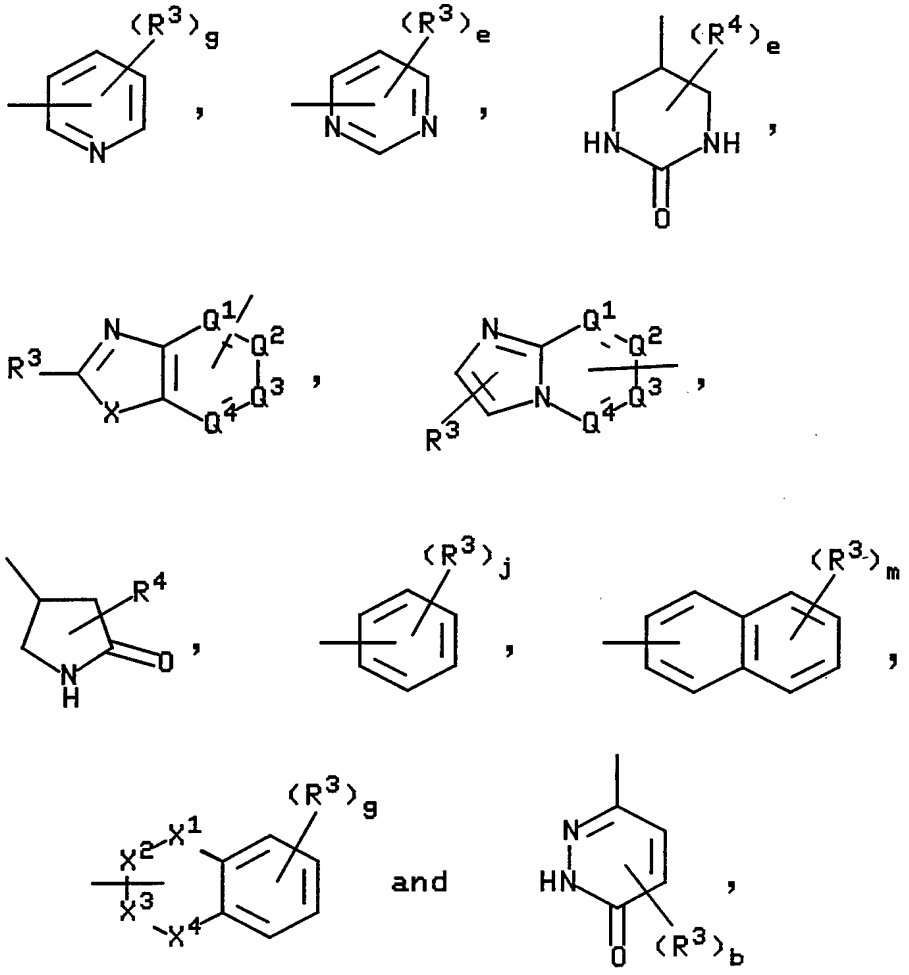


where Q^1, Q^2, Q^3, and Q^4 are independently N, CH or, when also bonded to B, C and provided that at least two of Q^1, Q^2, Q^3, and Q^4 are not N;

X is selected from the group consisting of O, NR^4 and S;

and X^1, X^2, X^3 and X^4 are independently selected from the group consisting of O, NR^4, S, C=O, CH_2 and, when also bonded to B, CH;

b is an integer from 1 to 2;

e is an integer from 1 to 3;

g is an integer from 1 to 4;

j is an integer from 1 to 5;

m is an integer from 1 to 7;

each R^3 is independently selected from the group consisting of hydrogen, halogen,

$(C_1$-$C_6)$alkyl, $CH(R^7)CO_2R^4$, $(C_1$-$C_6)$alkoxy, CO_2R^4, $CONR^4R^5$, CONHOH, $CH_2NR^4R^5$, NR^4R^5, nitro, hydroxy, CN, SO_3H, phenylalkyl having 1 to 4 carbons in the alkyl portion, $SO_2NR^4R^5$, $N(SO_2R^8)_2$ and $NHSO_2R^8$,

where R^4 for each occurrence is independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, phenyl optionally substituted with $(C_1$-$C_4)$alkyl or halogen, $CH(R^7)CO_2R^6$, $(C_3$-$C_7)$cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion and dialkylaminoalkyl having a total of 5 carbons in the dialkylamino portion and having 2 to 5 carbons in the alkyl portion where R^6 is as defined above,

R^5 for each occurrence is independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion, phenyl, pyridyl, pyrimidyl, thiazolyl and oxazolyl,

or R^4 and R^5 are taken together with the nitrogen to which they are attached and form an optionally substituted saturated or unsaturated 5- or 6-membered ring, a saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms, or a quinoline ring optionally substituted with fluoro,

where said optionally substituted saturated or unsaturated 5- or 6-membered ring may be mono- or di-substituted and each substituent is independently selected from the group consisting of alkyl having 1 to 4 carbons, CO_2R^7 wherein R^7 is as defined below, $CONH_2$, $CON(CH_3)_2$, oxo, hydroxy, NH_2 and $N(CH_3)_2$, and said saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms has the second heteroatom selected from the group consisting of O, S, NH, NCH_3, $NCOCH_3$ and NCH_2Ph;

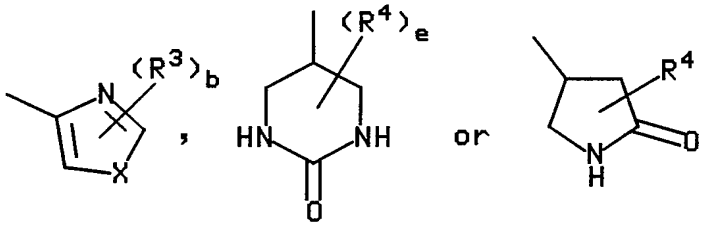
R^7 for each occurrence is independently selected from the group consisting of hydrogen and $(C_1$-$C_4)$alkyl;

and R^8 is selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, phenyl and phenyalkyl having 1 to 4 carbons in the alkyl portion;

with the proviso that:

when R^1 is methyl or ethyl; R^2 is (C_7-C_9)polycycloalkyl or indanyl; A, B and Y are covalent bonds; X is N; and R^3 is hydrogen;

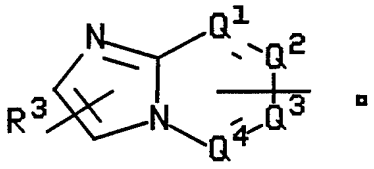
then Z is not



and with the further proviso that:

when R^1 is methyl or ethyl; R^2 is (C_7-C_9)polycycloalkyl or indanyl; A, B and Y are covalent bonds; Q^1, Q^2, Q^3, and Q^4 are CH or, when bonded to B, C; and R^3 is hydrogen;

then Z is not



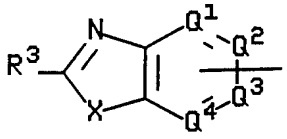
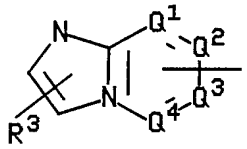
As used throughout this specification and the appendant claims, the terms "alkyl" and "alkoxy" include both straight chain and branched groups;

the term "halogen" includes fluoro, chloro and bromo; and

the symbol "Ph" in the term "NCH_2Ph" means phenyl.

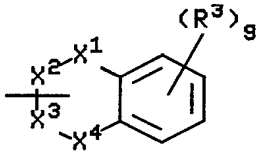
Those members of the substituent Z which are bicyclic are attached to the remainder of the compound of formula (I) through the ring of the Z substituent in which the bond is drawn.

As will be readily apparent to one skilled in the art, when Z is either

 or  , and one or more of Q^1, Q^2 Q^3 and

Q^4 is N, Z cannot be bonded through one of its ring nitrogen atoms to the rest of the molecule.

Further, it will also be readily apparent to one skilled in the art, when Z is

 and one or more of X^1, X^2, X^3 and X^4 is O, S, C=O or CH_2, Z cannot

be bonded through one of the above-named atoms or groups to the rest of the molecule.

A preferred group of compounds is that group of compounds of formula (I), above, wherein

R^1 is selected from the group consisting of methyl and difluoromethyl;

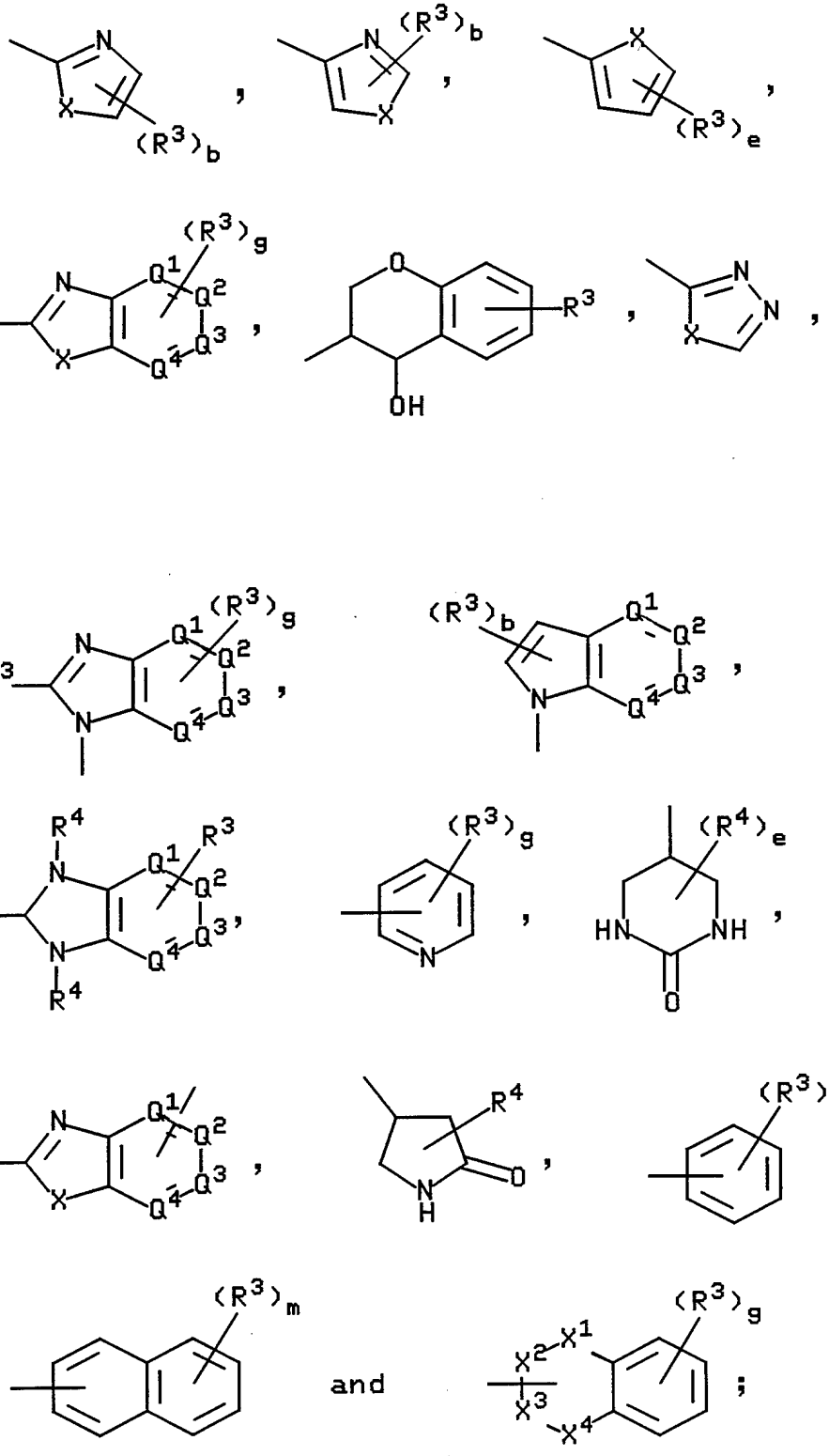
R^2 is selected from the group consisting of $(C_3$-$C_7)$cycloalkyl, $(C_6$-$C_9)$polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion and phenoxyalkyl having 2 to 6 carbons in the alkyl portion;

A is selected from the group consisting of a covalent bond, $(C_1$-$C_5)$alkylene and $(C_2$-$C_5)$alkenyl;

B is selected from the group consisting of a covalent bond, phenylene optionally substituted with $(C_1$-$C_4)$alkoxy, $(C_1$-$C_5)$alkylene and $(C_2$-$C_5)$alkenyl;

Y is selected from the group consisting of a covalent bond, O and NR^6;

Z is selected from the group consisting of



and

each R^3 is independently selected from the group consisting of hydrogen, halogen, $(C_1$-$C_6)$alkyl, $CH(R^7)CO_2R^4$, $(C_1$-$C_6)$alkoxy, CO_2R^4, $CONR^4R^5$, nitro, hydroxy, $N(SO_2R^8)_2$ and $NHSO_2R^8$,

where R^4 for each occurrence is independently selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl,

R^5 is selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl,

and Q^1, Q^2, Q^3, Q^4, X, X^1, X^2, X^3, X^4, b, e, g, j, m, R^6 and R^8 are as defined above.

A more preferred group of compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl;

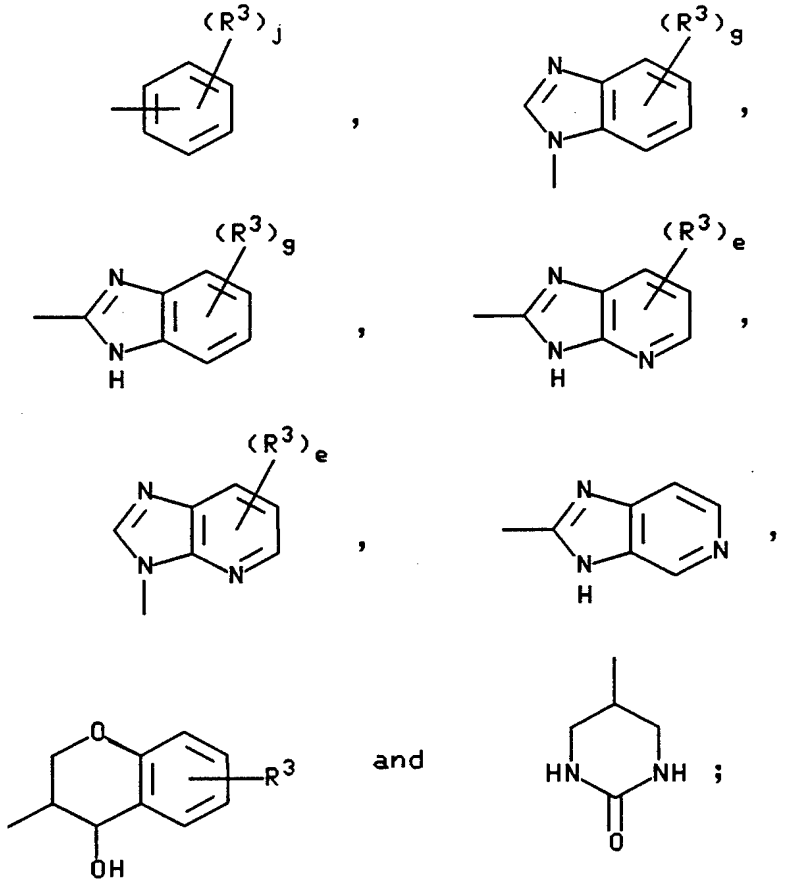
R^2 is selected from the group consisting of $(C_3$-$C_7)$cycloalkyl, $(C_6$-$C_9)$polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion;

A is selected from the group consisting of a covalent bond and methylene;

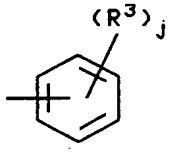
B is selected from the group consisting of a covalent bond, methylene and phenylene;

Y is selected from the group consisting of a covalent bond and O;

Z is selected from the group consisting of

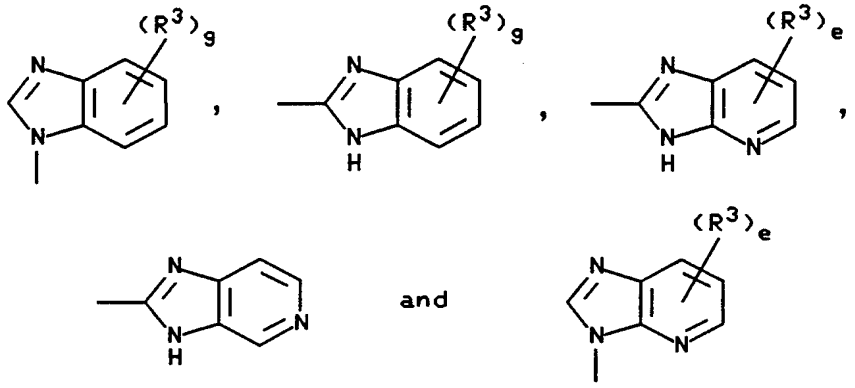


where R^3, e, g and j are as defined above.

Another group of preferred compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl; R^2 is selected from the group consisting of $(C_3\text{-}C_7)$cycloalkyl, $(C_6\text{-}C_9)$polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A, B and Y are a covalent bond; and Z is  , wherein R^3 and j are as defined above for formula (I).

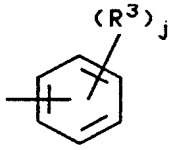
Another group of preferred compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl; R^2 is selected from the group consisting of $(C_3\text{-}C_7)$cycloalkyl,

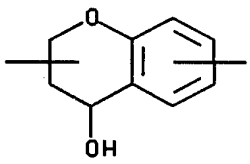
(C_6-C_9)polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A, B and Y are a covalent bond; and Z is selected from the group consisting of



and

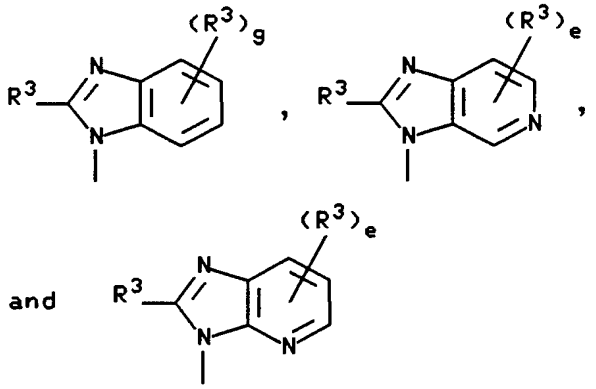
wherein R^3, g and e are as defined above for formula (I).

Yet still another group of preferred compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl; R^2 is selected from the group consisting of (C_3-C_7)cycloalkyl, (C_6-C_9)polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A is methylene; B is a covalent bond; Y is O; and Z is  , wherein R^3 and j are as defined above for formula (I).

Further, another group of preferred compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of methyl and difluoromethyl; R^2 is selected from the group consisting of (C_3-C_7)cycloalkyl, (C_6-C_9)polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion; A is methylene; B and Y are a covalent bond; and Z is  , wherein R^3 and g are as defined above for formula (I).

Furthermore, another group of preferred compounds is that group of compounds of formula (I), above, wherein R^1 is selected from the group consisting of

methyl and difluoromethyl; R^2 is selected from the group consisting of (C_3-C_7)cycloalkyl, (C_6-C_9)polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion and phenoxyalkyl having 2 to 6 carbons in the alkyl portion; A is methylene; B is phenylene; Y is O and Z is selected from the group consisting of



and

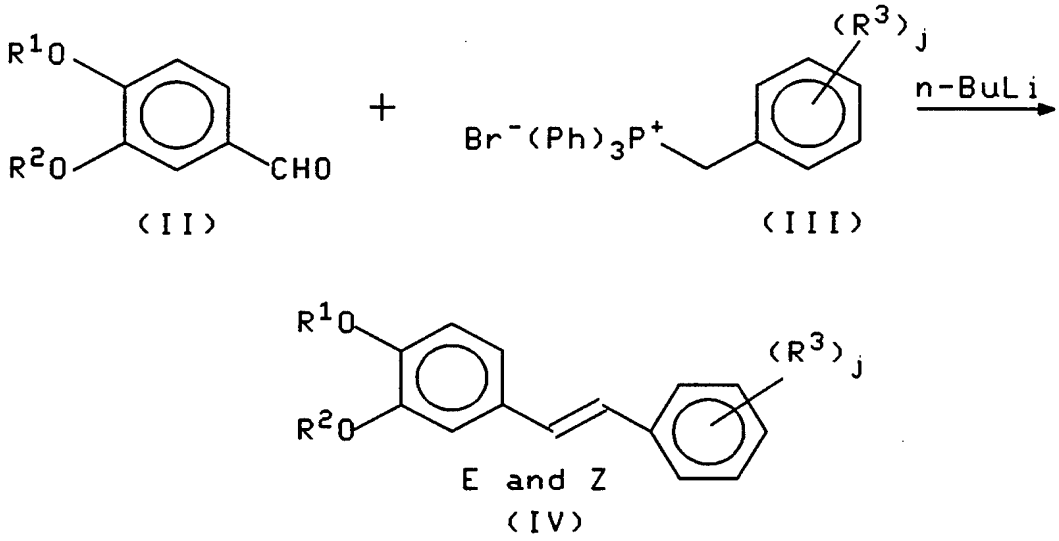
wherein R^3, g and e are as defined above for formula (I).

The starting materials and reagents required for the synthesis of the compounds of the present invention are readily available, either commercially, according to literature methods, or by methods exemplified in Preparations below.

Detailed Description of the Invention

The compounds of the invention can be prepared by a number of different processes according to the invention.

(a) In one process certain compounds of the formula (IV) can be prepared by the Wittig synthesis, according to the following reaction scheme:



wherein R^1, R^2, R^3 and j are as defined above for formula (I).

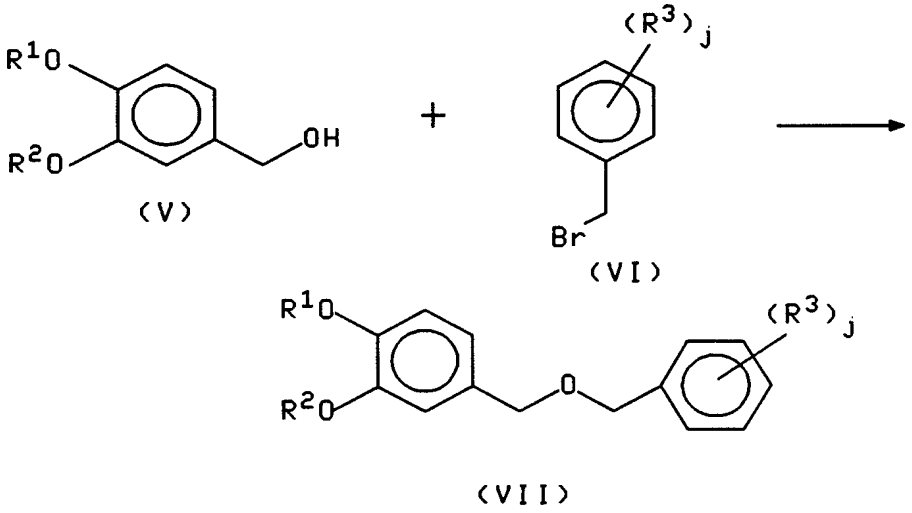
In a typical procedure, approximately one equivalent of the phenylphosphonium bromide (III), dissolved or suspended in dry THF, is treated with about 1.1 equivalents of 2.5M n-BuLi in hexane. This mixture is allowed to stir at about -78°C for about one hour. Then approximately one equivalent of the aldehyde (II), dissolved in anhydrous THF, is added to the formed yilide solution at about -78°C. After about one hour of stirring at about -78°C, the reaction mixture is allowed to warm to room temperature over about 18 hours. The reaction is worked-up by pouring it into water and extracting twice with a solvent such as ethyl acetate. The ethyl acetate is evaporated and the crude product is chromatographed on silica gel using 15% ether/hexanes as the eluant to yield the desired compound (IV). Both the cis and trans isomers of (IV) are isolated.

(b) In another process, a compound of the formula (IV), where j is 1 and the R^3 is either a methyl or an ethyl ester, is saponified to yield the analogous acid. In a typical procedure one equivalent of an ester of the formula (IV) is dissolved in a protic solvent, such as methanol. The ester is then mixed with about 1.5 to 10 equivalents (typically 2 equivalents) of 1N NaOH and heated at reflux temperature for about 0.5 hours to 5 hours (typically 1.5 hours). The reaction mixture is poured into water and washed once with a solvent, such as ethyl acetate. The aqueous layer is acidified to about pH 4 typically with HCl (aq) and extracted 3 times with ethyl acetate. The pure

desired product can be obtained by standard methods known to those skilled in the art such as crystallization or column chromatography on silica gel.

(c) In yet another process, a compound of the formula (IV) having the double bond can be hydrogenated to yield the corresponding alkylene analog. In a typical procedure about one equivalent of the compound (IV) is mixed with about 0.2 g to 1 g of 10% Pd/C in a mixture of protic and ether solvents, such as methanol and tetrahydrofuran. The mixture is placed in a Parr apparatus and pressurized with about 10 to 55 psi H_2, usually about 20 psi H_2, and shaken at room temperature (although the temperature may be raised as required) for about 1 to 24 hours, typically about 2 hours. The reaction mixture is filtered through celite to remove the catalyst and purified by chromatography on silica gel.

(d) In an alternative process, certain compounds of formula (VII) can be prepared by the Williamson synthesis, according to the following general reaction scheme:

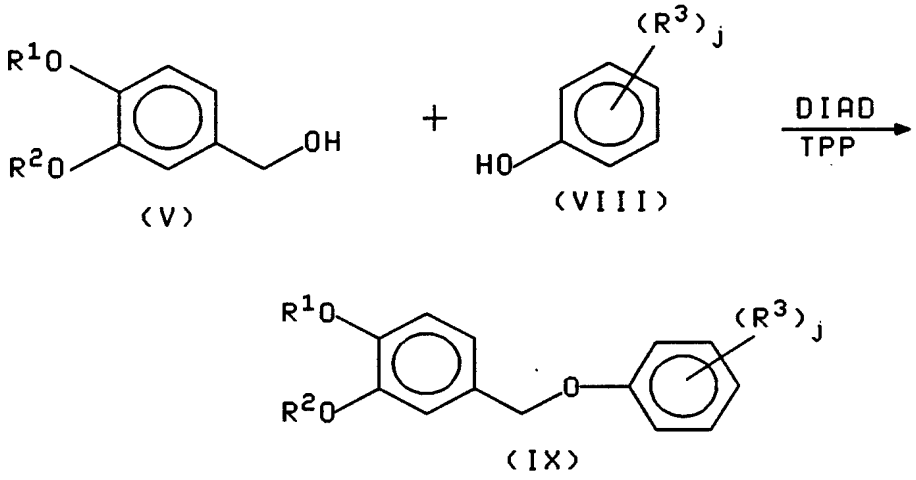


wherein R^1, R^2, R^3 and j are as defined above for formula (I).

In a typical procedure, about 1 to 2 equivalents, typically about 1.05 equivalents, of a 60% oil dispersion of NaH is added to a solution of the alcohol of formula (V) at room temperature. The alcohol of formula (V) is usually dissolved in dry dimethyl-formamide. The mixture is stirred for about 0.5 to 2 hours, typically about 1 hour, at room temperature, at which time the bromo compound of formula (VI) is added. The reaction mixture is stirred and heated to 100-125°C for about 24 hours to 72 hours. The

reaction is worked-up by pouring it into water and extracting twice with ethyl acetate followed by purification by chromatography on silica gel.

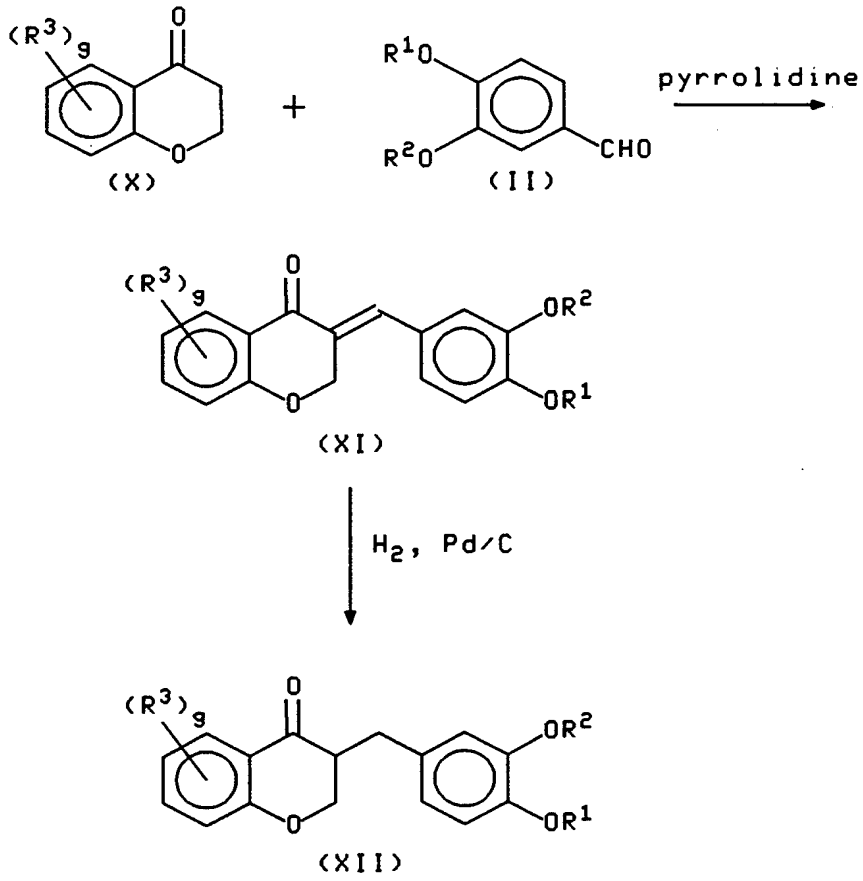
(e) In a further process, certain compounds of general formula (IX) can be prepared by a Mitsunobu type reaction, according to the following general reaction scheme:



wherein R^1, R^2, R^3 and j are as defined above for formula (I).

In a typical procedure, about 1 to 5 equivalents, typically 1.2 equivalents, of diisopropylazodicarboxylate (DIAD) or diethylazodicarboxylate (DEAD) is added to a mixture of about one equivalent of the alcohol (V), about one equivalent of the phenol (VIII) and about 1.1 equivalents of triphenylphosphine (TPP). All of the reactants are dissolved in a dry solvent, such as tetrahydrofuran. The reaction is stirred at room temperature for about 6 to 24 hours, typically 18 hours. The solvent is evaporated and the crude oil is purified by column chromatography on silica gel to yield the compound of formula (IX).

(f) In another process, certain compounds of the formula (XI) are prepared by the following general reaction scheme:



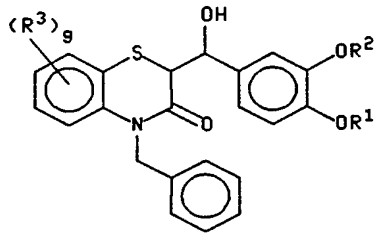
wherein R^1, R^2, R^3 and g are as defined above for formula (I).

About 1 equivalent of a secondary amine base, such as pyrrolidine is added to a room temperature solution of about 1 equivalent of the appropriately substituted chromanone (X) and about 1 equivalent of the necessary aldehyde (II) in a protic solvent such as methanol. The mixture is stirred for about 6 to 24 hours, usually 18 hours. The mixture is filtered to give the desired product as a solid. The compound of formula (XI) is then purified by either crystallization or by column chromatography. The compound of formula (XII) is obtained by hydrogenating compound (XI) analogous to method (c) above.

(g) In a further process, the ketone moiety of the chromanone compound of formula (XII) described hereinabove in method (f) can be reduced to the corresponding alcohol with a reducing agent such as $NaBH_4$. Approximately 0.8 equivalents of sodium

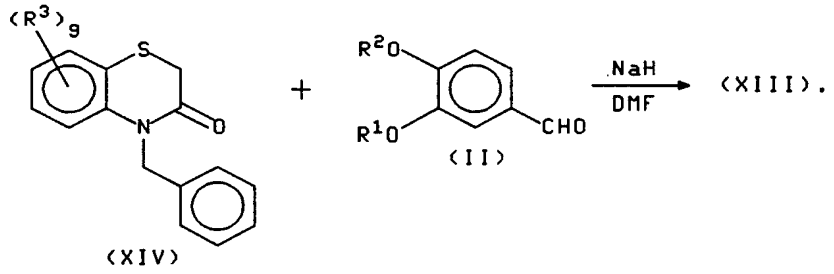
borohydride is added to a solution of approximately 1 equivalent of the chromanone (XII) and about 1 equivalent of $CeCl_3 \cdot 7\ H_2O$ in methanol and tetrahydrofuran. The temperature of the solution is usually about -20°C to -78°C, preferably -50°C. The reaction mixture is allowed to warm to room temperature over about 18 hours. The reaction is worked up by diluting with ethyl acetate and washing once each with NH_4Cl (aqueous), H_2O and brine. It is then dried over Na_2SO_4 and concentrated. The crude product is purified by chromatography on silica gel.

(h) Certain compounds having the general formula



(XIII)

, wherein R^1, R^2, R^3 and g are as defined above for formula (I), may be synthesized according to the following scheme:

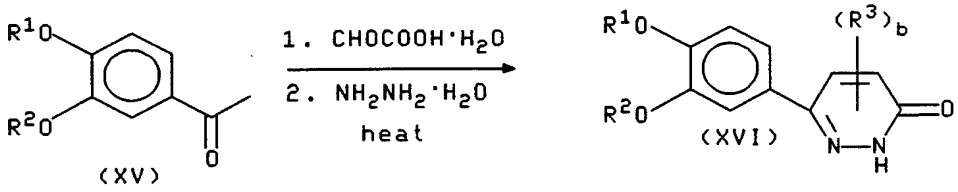


A solution of about one equivalent of (XIV) in dry DMF is added dropwise to a suspension of about 1.1 equivalents of NaH in dry DMF at about 0°C. The solution is stirred at about 0°C for about 30 minutes when a one equivalent solution of (II) in dry DMF is added. The mixture is allowed to come to room temperature over about 18 hours. The mixture is poured into water and acidified to pH 1. The resulting precipitate is filtered and dried. Further purification is done by chromatography on silica gel.

(i) In yet another process, an alcohol of formula (XIII) described in method (h), above, may be dehydrated to give the corresponding alkenyl analog. In a typical procedure, about 1.5 equivalents of oxalyl chloride is added to a solution of about 2

equivalents of dry DMSO in dry methylene chloride at about -50°C to -78°C, preferably at -65°C. A solution of the alcohol of the formula (XIII) described in method (h), above, dissolved in dry methylene chloride, is added to the cold solution of DMSO. This mixture is allowed to warm with stirring to about -30°C over about 1 hour. It is then cooled to about -78°C and 2 to 10 equivalents of triethylamine is added. This mixture is stirred at room temperature for about 1 hour. The reaction is worked-up by standard methods known to those skilled in the art and purified either by column chromatography on silica gel or by crystallization.

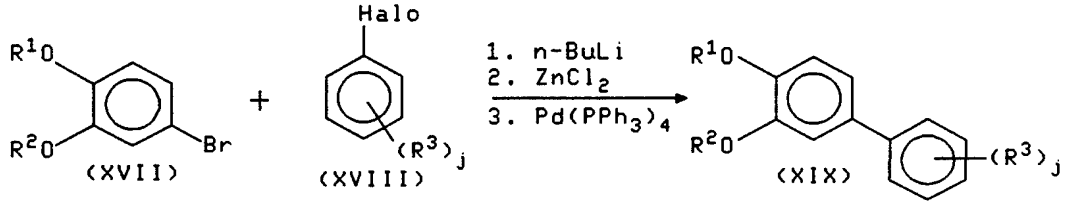
(j) Certain compounds of the formula (XVI) may be synthesized according to the scheme shown below:



wherein R^1, R^2, R^3 and b are as defined above for formula (I).

In a typical procedure, a ketone of the formula (XV) is heated with glyoxylic acid monohydrate at about 100°C to 150°C, preferably about 120°C. The reaction is cooled to about 60°C and about 2 ml of H_2O is added. About 20 to 30 drops of concentrated NH_4OH and about 1 equivalent of hydrazine monohydrate are added. The mixture is then heated at reflux for about 2 hours. It is cooled to room temperature and about 5 ml of water is added. The mixture is stirred for about 50 to 72 hours, preferably for about 60 hours. The suspension is filtered and purified by column chromatography on silica gel followed by crystallization.

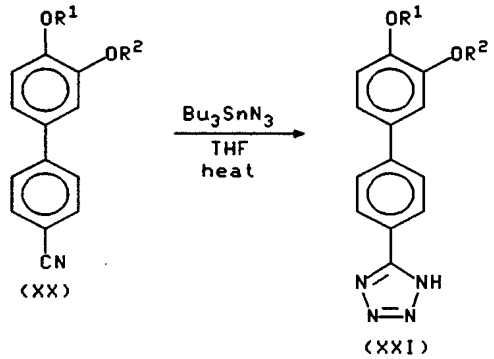
(k) Certain compounds of formula (XIX) are prepared by palladium cross coupling according to the following scheme:



wherein R^1, R^2, R^3 and j are as defined above for formula (I).

A typical procedure is carried out by taking a solution of about one equivalent of the appropriate bromo compound (XVII), dissolved in dry THF, and cooling it to about -78°C. About 1.1 equivalents of a 2.5M solution of n-BuLi is added to the bromo compound and stirred for about 40 minutes at about -78°C. About 1.2 equivalents of a 1.0M solution of $ZnCl_2$ in ether is added and the reaction mixture allowed to warm to room temperature over about 35 minutes. A catalytic amount, about 0.05 equivalents, of tetrakis(triphenylphosphine)palladium(0) and the required halo compound (XVIII), wherein "Halo" is I, Br or Cl but preferably I or Br, are added to the reaction mixture and allowed to stir for about 12 hours. The reaction is concentrated and chromatographed on silica gel to yield the desired compound of formula (XIX).

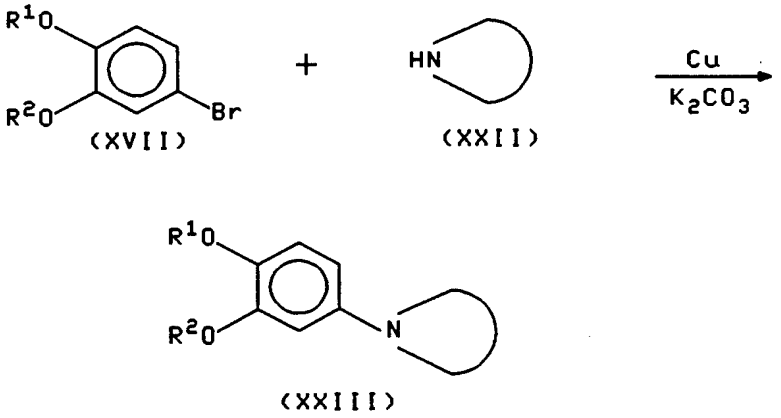
(l) Yet another process which is utilized to prepare certain compounds of formula (I) involves the formation of a tetrazole from a cyano group using Bu_3SnN_3, according to the general scheme:



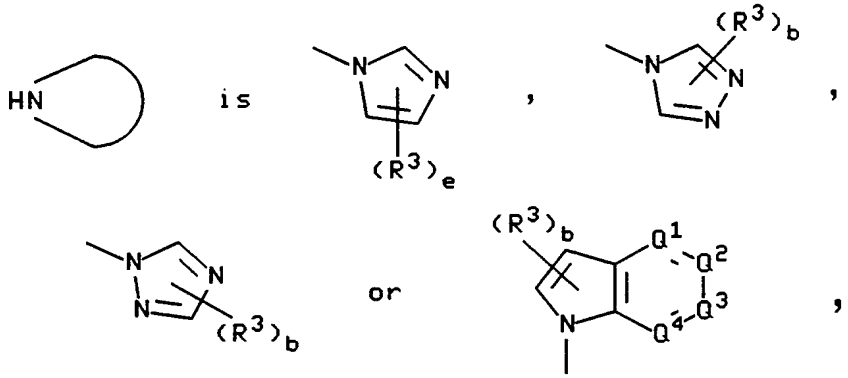
wherein R^1 and R^2 are as defined above for formula (I).

In a typical method, about one equivalent of the cyano compound of formula (XX), dissolved in dry THF, is mixed with a dry THF solution of Bu_3SnN_3 and the mixture heated at reflux temperature for about 4 days. The mixture is cooled to room temperature, concentrated and chromatographed on silica gel to afford the desired tetrazole (XXI).

(m) Certain compounds of formula (I) may also be synthesized by reaction of bromo compounds (XVII) with amino compounds (XXII), according to the general reaction scheme:



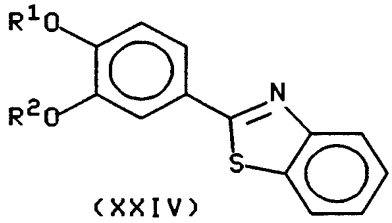
wherein R^1 and R^2 are as defined above for formula (I) and



wherein Q^1, Q^2, Q^3, Q^4, R^3, b and e are as defined above for formula (I).

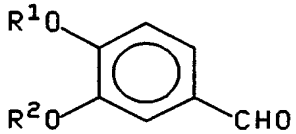
In a typical procedure, a mixture of about one equivalent of all of the reagents shown in the above scheme are heated to about 110-150°C for about 24 hours. The

mixture is cooled to room temperature and worked-up according to standard methods well known to those skilled in the art. Chromatography on silica gel yields the desired compound of general formula (XXIII).

(n) The following procedure is employed to synthesize compounds of the formula  wherein R^1 and R^2 are as defined above for

(XXIV)

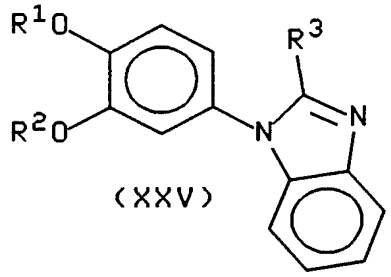
formula (I).

About one equivalent of an aldehyde of the formula  is mixed with

(II)

about one equivalent of an optionally substituted 2-mercaptoaniline and heated on a steam bath for about 15 minutes. The reaction mixture is cooled and dissolved in a methanol solution of 10% $FeCl_3$ and stirred overnight. The reaction is diluted with H_2O and extracted with chloroform. The chloroform is evaporated and the residue is chromatographed to yield the desired benzothiazole derivatives of formula (XXIV).

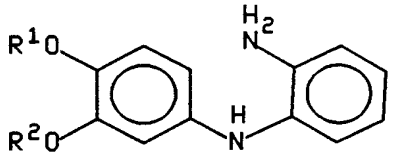
(o) The following procedure is used to synthesize compounds of the formula



(XXV)

wherein R^1, R^2 and R^3 are as defined above for formula (I).

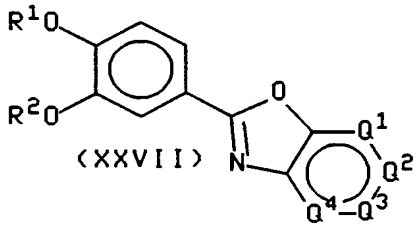
About one equivalent of a compound of the formula



(XXVI)

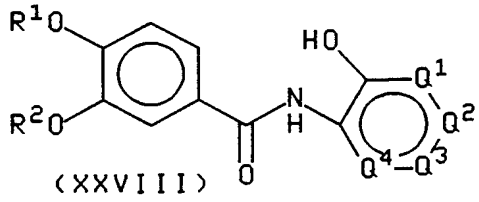
is mixed with ethyl formate and approximately 25 ml of formic acid and heated at about 100°C for about 18 hours. The solvent is evaporated and the residue chromatographed on silica gel to yield the desired benzimidazole derivatives of formula (XXV).

(p) Compounds having the general formula



(XXVII)

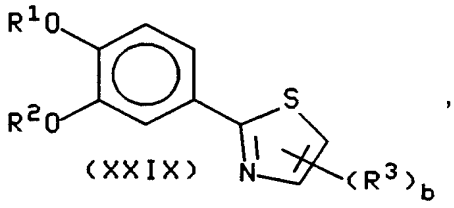
, wherein R^1, R^2, Q^1, Q^2, Q^3 and Q^4 are as defined above for formula (I), are synthesized by the following general method. A compound of the general formula



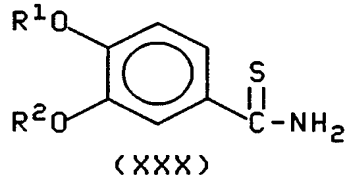
(XXVIII)

is mixed with $POCl_3$ and

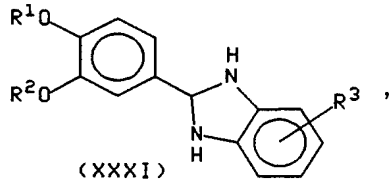
heated at reflux for about 24 hours. Excess $POCl_3$ is evaporated and the crude product is purified by chromatography on silica gel to yield the desired oxazolo derivatives of formula (XXVII).

(q) Compounds having the general formula 

(XXIX),

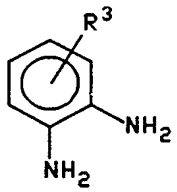
wherein R^1, R^2, R^3 and b are as defined above for formula (I), are synthesized by the following general method. A compound of the general formula 

(XXX) is mixed with chloroacetaldehyde in ethanol and heated at reflux temperature for about 6 hours. The volatile components are evaporated and the residue is purified by chromatography on silica gel to yield the desired thiazole derivative of formula (XXIX).

(r) Compounds having the general formula 

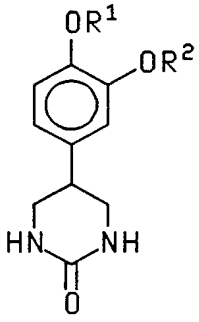
(XXXI),

wherein R^1, R^2 and R^3 are as defined above for formula (I), are synthesized by the following general method. A compound of the general formula (II) is mixed with an

appropriate compound of the general formula  and the mixture heated

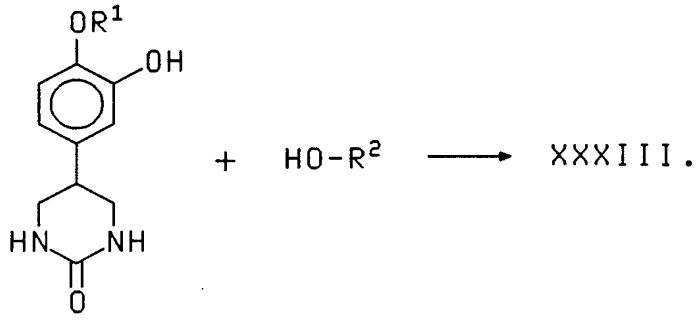
(XXXII)

to about 120°C for about 1 to 6 hours. The resulting residue is chromatographed on silica gel to yield the desired derivative of formula (XXXI).

(s) Compounds having the general formula  , wherein R^1 and

(XXXIII)

R^2 are as defined above for formula (i), are synthesized by one of the two general methods described below. The first general method is a Mitsinobu type reaction illustrated by the general scheme



(XXXIV)

The reaction is carried out analogously to the description provided in general method (e) above.

The second general method is carried out according to the following general scheme: XXXIV + Halo-R^2 ⟶ XXXIII , wherein "Halo" is Cl, Br or I.

A compound of general formula (XXXIV) is dissolved in anhydrous DMSO. To this mixture approximately 2.5 equivalents of anhydrous K_2CO_3 and the appropriate halide (Halo-R^2) are added. The reaction mixture is heated to about 80°C for about 2-5 hours. After conventional work-up of the reaction mixture, the desired product is isolated by chromatography on silica gel.

The synthetic methods outlined above in methods a to s together with the following Examples describe methods which were and can be employed to prepare the compounds of this invention.

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit phosphodiesterase IV (PDE_4) and, consequently, demonstrate their effectiveness for treating inflammatory diseases is shown by the following in vitro assay.

BIOLOGICAL ASSAY

(Human lung PDE_{IV})

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at 4°C. The supernatant is filtered twice through a 0.22 μm filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE_{IV} activity, determined by [^{3}H]cAMP hydrolysis and the ability of a known PDE_{IV} inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

Compounds are dissolved in DMSO at a concentration of 10 mM and diluted 1:25 in water (400 μM compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. Final DMSO concentration in assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as final concentrations in assay tube).

i) 25 μl compound or DMSO (1%, for control and blank)

ii) 25 μl pH 7.5 Tris buffer

iii) [^{3}H]cAMP (1 μM)

iv) 25 μl PDE_{IV} enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)/0.1M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an Affi-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [^{3}H]cAMP is washed with 2 x 6 ml washing buffer, and [^{3}H]5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [^{3}H].

% Inhibition is determined by the formula:

$$\% \text{ Inhibition} = 1 - \frac{\text{average cpm (test compound) - average cpm (blank)}}{\text{average cpm (control) - average cpm (blank)}}$$

IC_{50} is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [^{3}H]cAMP to [^{3}H]5'AMP.

Pharmaceutically-acceptable acid addition salts of the compounds of this invention include, but are not limited to, those formed with HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3CO_2H, gluconic acid, tartaric acid, maleic acid and succinic acid. In the case of those compounds of the formula (I) which contain a further basic nitrogen, it will, of course, be possible to form diacid addition salts (e.g., the dihydrochloride) as well as the usual monoacid addition salt. Pharmaceutically-acceptable cationic salts of the compounds of this invention include, but are not limited to, those of sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine and diethanolamine.

For administration to humans in the curative or prophylactic treatment of inflammatory conditions, oral dosages of the compounds are generally in the range of from 0.1-100 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.1 to 50 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovales either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances; for example, enough salts or glucose to make the solution isotonic.

Thus in a further aspect the invention provides pharmaceutical compositions comprising a compound of the formula (I), or pharmaceutically acceptable salts thereof, together with a pharmaceutically acceptable diluent or carrier.

This invention also provides a method of inhibiting phosphodiesterase IV (PDE_{IV}) in a mammal in need thereof which method comprises administering to said mammal a phosphodiesterase IV inhibiting amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof.

This invention further provides a method of treating an inflammatory condition in mammals which comprises administering to said mammal an antiinflammatory amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof.

Further still, this invention provides a method of treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis

or shock in a mammal which comprises administering to said mammal an effective amount of a compound or a pharmaceutically acceptable salt thereof.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

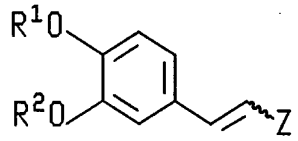
EXAMPLE 1

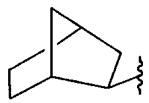
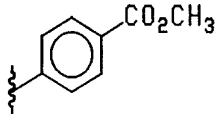
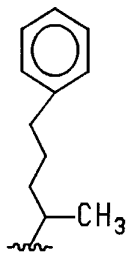
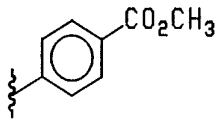
Methyl 3-[2-[3-(cyclopentyloxy)-
4-methoxyphenyl]ethenyl] benozate

To a -78°C suspension of (1.55 g, 3.16 mmol, 1.05 eq) 3-carbomethoxybenzyltriphenylphosphonium bromide in 50 ml of anhydrous tetrahydrofuran (1.20 ml of 2.5M, 3.01 mmol, 1.0 eq) n-BuLi in hexane was added dropwise. After stirring 45 minutes at -78°C, a solution of (0.663 g, 3.01 mmol, 1.0 eq) 3-cyclopentyloxy-4-methoxybenzaldehyde in 20 ml of anhydrous tetrahydrofuran was added dropwise, and the reaction mixture was allowed to warm to room temperature over 18 hours. The reaction mixture was poured into 300 ml H_2O and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with brine, dried over Na_2SO_4, and concentrated to yield 2.12 g of a yellow oil. Silica gel chromatography eluting with 15% ether-hexane afforded 386 mg, 36%, of the cis isomer and 380 mg, 36%, of the trans isomer. Mass spectra: $M^+ = 352$.

EXAMPLES 2-3

Reaction of the appropriate aldehyde with the requisite aryltriphenylphosphonium bromide, analogous to the procedure of Example 1, afforded the following compounds having the general formula:



Ex.#	Isomer	R^1	R^2	Z	M.P. °C	Analysis					
						Calculated (%)			Found (%)		
						C	H	N	C	H	N
2	Cis & Trans Mixture	CH_3			65-67°	76.17	6.93	--	76.15	7.03	--
3	Cis & Trans Mixture	CH_3			Oil	78.11	7.02	--	78.23	7.21	--

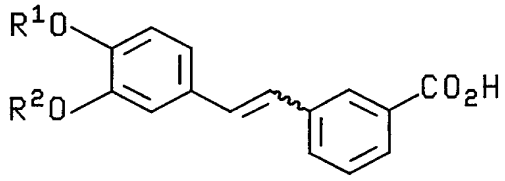
EXAMPLE 4

3-[2-[3-(Cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoic Acid

A mixture of (335 mg, 0.951 mmol, 1.0 eq) methyl, 3-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]ethenyl]benzoate in 8 ml methanol and 1.9 ml (1.90 mmol, 2.0 eq) of 1N NaOH was heated to reflux for 1.5 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, poured into 100 ml H_2O, basified to pH 12, and washed once with ethyl acetate. The aqueous layer was acidified to pH 4 and extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed once with H_2O, once with brine, dried over Na_2SO_4, and concentrated to yield 295 mg of white waxy crystals. Recrystallization from ethyl acetate-hexane afforded 110 mg, 34%, of the cis isomer as white crystals. M.P.: 93-94°C. Elemental Analysis: Calc'd for $C_{21}H_{22}O_4$: Calc'd: C, 74.53; H, 6.55. Found: C, 74.32; H, 6.68.

EXAMPLES 5-6

Reaction of the appropriate methyl ester, analogous to the procedure of Example 4, afforded the following compounds:



Ex.#	Isomer	R^1	R^2	M.P. °C	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
5	Trans	CH_3		137-138°	74.53	6.55	74.27	6.39
6	Cis	CH_3		79-81°	--	--	--	--

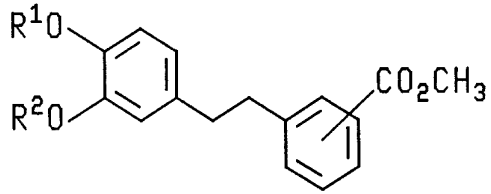
EXAMPLE 7

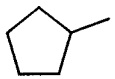
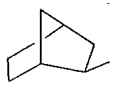
Methyl 4-[2-[4-methoxy-3-(1-methyl-4-phenylbutoxy)phenyl]ethyl]benzoate

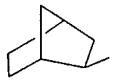
A mixture of (1.18 g, 2.74 mmol, 1.0 eq) methyl 4-[2-[4-methoxy-3-(1-methyl-4-phenylbutoxy)phenyl]ethenyl]benzoate and 0.600 g of 10% Pd/C in 30 ml methanol and 30 ml tetrahydrofuran was placed on a Parr hydrogenation apparatus and shaken under 20 psi H_2 at room temperature for 1.5 hours. The reaction mixture was filtered through celite, concentrated in vacuo, and flash chromatographed on a silica gel column eluting with 20% ether-hexane to afford 1.00 g, 84%, of a clear oil. Elemental Analysis Calc'd for $C_{28}H_{32}O_4$: Calc'd: C, 77.75; H, 7.46. Found: C, 77.55; H, 7.55.

EXAMPLES 8-10

Reaction of the appropriate alkenylaryl methyl ester, analogous to the procedure of Example 7, afforded the following compounds:



Ex.#	R^1	R^2	Position of CO_2CH_3	M.P. °C	Formula (MW)	Mass Spec (M+)	Analysis			
							Calculated (%)		Found (%)	
							C	H	C	H
8	CH_3		meta	oil	$C_{22}H_{26}O_4$ 354.4	354	--	--	--	--
9	CH_3		meta	oil	$C_{24}H_{28}O_4$ 380.4	380	75.77	7.42	75.58	7.68

Ex.#	R^1	R^2	Position of CO_2CH_3	M.P. °C	Formula (MW)	Mass Spec (M+)	Analysis			
							Calculated (%)		Found (%)	
							C	H	C	H
10	CH_3		para	72-74°	$C_{24}H_{28}O_4$ 380.4	380	--	--	--	--

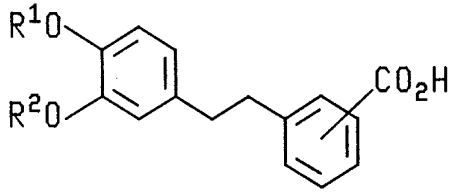
EXAMPLE 11

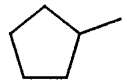
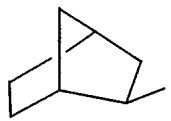
4-[2-[4-methoxy-3-(1-methyl-4-phenyl-butoxy)phenyl]ethyl]benzoic acid

Reaction of methyl, 4-[2-[4-methoxy-3-(1-methyl-4-phenylbutoxy)phenyl]ethyl]-benzoate, analogous to the procedure of Example 4, yielded the title compound, 735 mg, 91%, as white crystals. M.P.: 112°C. Elemental Analysis Calc'd for $C_{27}H_{30}O_4$: Calc'd: C, 77.48; H, 7.23. Found: C, 77.62; H, 7.36.

EXAMPLES 12-14

Reaction of the appropriate methyl ester, analogous to the procedure of Example 11, afforded the following compounds:



Ex.#	R^1	R^2	Position of CO_2H	M.P. °C	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
12	CH_3		meta	86-8°	74.09	7.11	74.21	7.16
13	CH_3		meta	105-7°	75.39	7.15	75.54	7.16

Ex.#	R^1	R^2	Position of CO_2H	M.P. °C	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
14	CH_3		para	149-50°	75.39	7.15	75.20	7.13

EXAMPLE 15

3-[[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]methyl]benzoic acid

Added (178 mg, 4.44 mol, 1.05 eq) 60% NaH to a room temperature solution of (1.05 g, 4.23 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenylmethanol in 20 ml anhydrous dimethylformamide. After stirring 45 minutes at room temperature, (1.45 g, 6.35 mmol, 1.5 eq) of methyl-3-bromomethylbenzoate was added. After 60 hours at room temperature, the reaction mixture was poured into 300 ml H_2O and extracted twice with ethyl acetate. The ethyl acetate extracts were washed twice with H_2O, once with brine, dried over Na_2SO_4, and concentrated to yield 2.33 g of a yellow oil. Silica gel chromatography eluting with 10%, then 20% ethyl acetate-hexane afforded 322 mg, 19%, of a colorless oil, methyl, 3-[[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]methyl]benzoate.

A mixture of (310 mg, 0.782 mmol, 1.0 eq) the above methyl ester (the colorless oil) in 10 ml methanol and 3 ml of 1N NaOH was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, poured into 150 ml H_2O and 25 ml ethyl acetate, acidified to pH 4.5, and extracted twice with ethyl acetate. The ethyl acetate extracts were washed once with H_2O, once with brine, dried over Na_2SO_4, and concentrated to yield 0.28 g of a pale yellow oil. Silica gel chromatography, eluting with 5% CH_3OH-CH_2Cl_2, followed by recrystallization from ether/petroleum ether afforded 217 mg, 73%, of white crystals. M.P.: 77-79°C. Elemental Analysis: Calc'd for $C_{23}H_{26}O_5$: Calc'd: C, 72.31; H, 6.86. Found: C, 72.30; H, 6.80.

EXAMPLE 16

2-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenylmethoxy]nicotinic acid

A mixture of (0.82 g, 3.3 mmol, 1.0 eq) (±)-3-exo-norbornyloxy-4-methoxybenzyl alcohol and (0.263 g, 6.6 mmol, 2.0 eq) NaH (60% oil dispersion) in 20 ml of anhydrous dimethylformamide was stirred at room temperature for 0.5 hours. 2-Chloronicotinic acid (0.52 g, 3.3 mmol, 1.0 eq) was added, and the reaction mixture heated to reflux for 24 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, dissolved in ethyl acetate and washed with 2N NaOH. The base wash was acidified to pH 5-6 and extracted with ethyl acetate. The ethyl acetate extracts were washed twice with H_2O, once with brine, dried over Na_2SO_4 and concentrated to yield

944 mg of a white semi-solid. Silica gel chromatography eluting with 2½%, then 4% CH_3OH-CH_2Cl_2 afforded 69 mg, 6%, of a white amorphous foam. M.P.: 50°C+(dec.).

EXAMPLE 17

6-[[3-(Bicyclo[2.2.1]-hept-2-yloxy)-4-methoxyphenyl]methoxy]-α-methyl-2-naphthaleneacetic acid

(±)-3-Exo-norbornyloxy-4-methoxybenzyl bromide (0.719 g, 2.31 mmol, 1.0 eq) was added to a mixture of (0.50 g, 2.31 mmol, 1.0 eq) α-methyl-2-(5-hydroxynaphthalene acetic acid and (1.12 g, 3.5 eq, 8.09 mmol) K_2CO_3 in 35 ml of anhydrous dimethylformamide. After stirring 18 hours at room temperature under N_2, the reaction mixture was poured into 350 ml of H_2O, acidified to pH 4-5 and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H_2O, once with brine, dried over Na_2SO_4, and concentrated in vacuo to yield a yellow-brown oil. Silica gel chromatography eluting with 2½% CH_3OH-CH_2Cl_2 gave 0.52 g of a white amorphous solid. Recrystallization from isopropanol-hexane yielded 0.47 g, 46%, of a light yellow crystal. M.P.: 125-128°C. Elemental Analysis: Calc'd for $C_{28}H_{30}O_5$: Calc'd: C, 75.31; H, 6.77. Found: C, 75.26; H, 7.01.

EXAMPLE 18

Methyl 3-[[3-(cyclopentyloxy)-4-methoxyphenyl]methoxy]benzoate

Diisopropylazodicarboxylate (1.2 ml, 5.99 mmol, 1.2 eq)was added to a mixture of (1.10 g, 4.99 mmol, 1.0 eq) 3-cyclopentyloxy-4-methoxybenzyl alcohol, (1.44 g, 5.49 mmol, 1.1 eq) triphenylphosphine, and (0.75 g, 4.99 mmol, 1.0 eq) methyl-3-hydroxybenzoate in 30 ml of anhydrous tetrahydrofuran. After stirring for 18 hours at room temperature the reaction mixture was concentrated in vacuo and chromatographed on a silica gel column, eluting with 10%, then 15% ethyl acetate-hexane to yield 897 mg, 50%, of a clear oil. High Resolution Mass Spectra: Calc'd 356.1624. Found: 356.1600.

EXAMPLE 19

Tetrahydro-5-[4-methoxy-3-(difluoromethoxy)phenyl]-2(1H)-pyrimidinone

Chlorodifluoromethane was bubbled into a solution of (102 mg, 0.459 mmol, 1.0 eq) of tetrahydro-5-(4-methoxy-3-hydroxyphenyl)-2(1H)-pyrimidinone and 64 mg (1.61 mmol, 3.5 eq) of NaOH in 3 ml of H_2O and 3 ml of 1,4-dioxane. After 1 hour at room temperature, the reaction mixture was heated to 60°C for 1.5 hours. Chlorodifluoromethane was bubbled in continuously. The reaction mixture was cooled to room

temperature, poured into 150 ml of H_2O and 75 ml of ethyl acetate, extracted twice with ethyl acetate. The ethyl acetate extracts were washed twice with 2N NaOH, once with brine, dried over Na_2SO_4, and concentrated to yield 13.5 mg of a white solid, which was recrystallized from ethyl acetate-hexane to afford 8.4 mg, 7%, of off-white crystals. M.P.: 215-216°C. Elemental Analysis: Calc'd for $C_{12}H_{14}N_2O_3F_2$: Calc'd: C, 52.95; H, 5.18; N, 10.29. Found: C, 52.88; H, 4.91; N, 10.13.

EXAMPLE 20

5-(3-(Bicyclo[2.2.1]hept-2-yloxy)-4-difluoro-methoxyphenyl)tetrahydro-2(1H)-pyrimidone

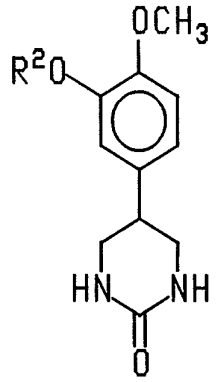
$Pb(OAc)_4$ (2.96 g of 95%, 6.67 mmol, 2.2 eq) was added portionwise to a slurry of (1.16 g, 3.03 mmol, 1.0 eq) 3-[3-bicyclo[2.2.1]hept-2-yloxy)-4-(difluoromethoxy)-phenyl]pentanediamide, in 50 ml anhydrous pyridine. After stirring 18 hours at room temperature, the reaction mixture was poured into 600 ml of H_2O and extracted four times with ethyl acetate. The ethyl acetate extracts were washed once with brine, dried over Na_2SO_4, and concentrated to yield 1.4 g of a yellow solid. Silica gel chromatography eluting with 2½%, then 3% CH_3OH-CH_2Cl_2 yielded 1.06 g of a white solid. Recrystallization from ethyl acetate-hexane afforded 598 mg, 56%, of white crystals. M.P.: 217-219°C. Elemental Analysis Calc'd for $C_{18}H_{22}N_2O_3F_2$: Calc'd: C, 61.35; H, 6.29; N, 7.95. Found: C, 61.53; H, 6.38; N, 7.81.

EXAMPLE 21

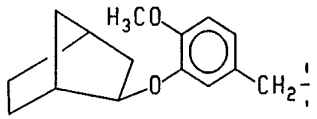
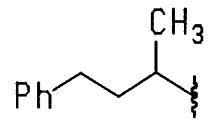
Tetrahydro-5-[3-(4-phenylbutoxy)-4-methoxyphenyl]-2(1H)-pyrimidinone

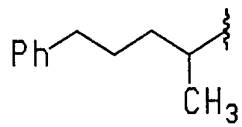
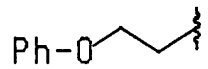
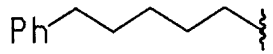
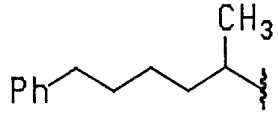
Diisopropylazodicarboxylate (1.1 ml, 5.70 mmol, 1.2 eq) was added to a mixture of (1.06 g, 4.75 mmol, 1.0 eq) tetrahydro-5-(3-hydroxy-4-methoxyphenyl)-2(1H)-pyrimidinone, (1.37 g, 5.23 mmol, 1.1 eq) triphenylphosphine, and (714 mg, 4.75 mmol, 1.0 eq) 4-phenyl-1-butanol in 20 ml of anhydrous tetrahydrofuran. After heating to reflux for 18 hours, the reaction mixture was cooled to room temperature, diluted with 350 ml ethyl acetate, washed twice with 1N NaOH, once with H_2O, once with brine, dried over Na_2SO_4, and concentrated to yield an orange solid. Silica gel chromatography eluting with 4% CH_3OH-CH_2Cl_2 yielded 527 mg of a white solid, which was recrystallized from ethyl acetate to afford 480 mg, 29%, of white needles. M.P.: 142-143°C. Elemental Analysis Calc'd for $C_{21}H_{26}N_2O_3$: Cal'd: C, 71.17; H, 7.40; N, 7.90. Found: C, 71.12; H, 7.32; N, 7.75.

EXAMPLES 22-27



Reaction of 2(1H)-pyrimidine, tetrahydro-5-(3-hydroxy-4-methoxyphenyl)- with the appropriate alcohol of the general formula R-OH, analogous to the procedure of Example 21, yielded the following compounds:

Ex.#	R^2	M.P. °C	Analysis					
			Calculated (%)			Found (%)		
			C	H	N	C	H	N
22		157-60°	69.01	7.13	6.19	67.58	6.76	6.33
23		152-4°	71.17	7.40	7.90	71.13	7.42	7.80

Ex.#	R^2	M.P. °C	Analysis					
			Calculated (%)			Found (%)		
			C	H	N	C	H	N
24		99-101°	--	--	--	--	--	--
25		147-9°	--	--	--	--	--	--
26		160-2°	71.72	7.66	7.60	71.17	7.49	7.48
27		90-2°	72.22	7.91	7.32	72.20	7.79	7.27

EXAMPLE 28

5-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]tetrahydro-1,3-bis(2-quinolinylmethyl)-2(1H)-pyrimidinone

NaH (63 mg, 1.58 mmol, 1.0 eq, 60% oil dispersion) was added to a mixture of (0.500 g, 1.58 mmol, 1.0 eq) 5-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]tetrahydro-2(1H)-pyrimidinone and (0.279 g, 1.58 mmol, 1.0 eq) 2-chloromethylquinoline in 12 ml of anhydrous dimethylformamide. After stirring for 18 hours at room temperature, the reaction mixture was diluted with 250 ml of H_2O and extracted with ethyl acetate. The ethyl acetate extract was washed once with H_2O, once with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a silica gel column, eluting with 2½% CH_3OH-CH_2Cl_2 to yield 50 mg of a solid, which was recrystallized from ethyl acetate-hexane to afford 45 mg, 5%, of a white crystalline solid. M.P.: 135-136°C.

EXAMPLE 29

1-[(7-Chloro-2-quinolinyl)methyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone

4-[3-Cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone (1.00 g, 3.63 mmol, 1.0 eq) was added to a room temperature suspension of (145 mg, 3.63 mmol, 1.0 eq) NaH (60% oil dispersion) in 30 ml of anhydrous DMF. After stirring at room temperature for 1 hour, (0.77 g, 3.63 mmol, 1.0 eq) 2-chloromethyl-7-chloroquinoline was added, and the reaction mixture was allowed to stir at room temperature for 60 hours. The reaction mixture was then diluted with 250 mL H_2O and extracted with ethyl acetate. The ethyl acetate extract was washed twice with H_2O, once with brine, dried over Na_2SO_4 and concentrated to yield a yellow oil. Silica gel chromatography eluting with 5% CH_3OH/CH_2Cl_2 followed by recrystallization from ethyl acetate-hexane yielded 0.61 g, 37%, of white crystals. M.P.: 106-107°C. Elemental Analysis Calc'd for $C_{26}H_{27}N_2O_3Cl$: Calc'd: C, 69.15; H, 6.03; N, 6.21. Found: C, 69.22; H, 5.75; N, 6.15.

EXAMPLE 30

1-(6-Fluoroquinolin-2-ylmethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidinone

Reaction of 4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidinone with 2-chloromethyl-6-fluoroquinoline, analogous to the procedure of Example 29, yielded the title compound. M.P.: 65-68°C. High Resolution Mass Spectra: Calc'd: 434.1983. Found: 434.2005.

EXAMPLE 31

[(3-Benzoic acid)methyl-4-(3-cyclopentyl-oxy)-4-methoxyphenyl]-2-pyrrolidinone

NaH (145 mg, 3.63 mmol, 1.0 eq, 60% oil dispersion) was added to a room temperature solution of (1.00 g, 3.63 mmol, 1.0 eq) of [3-(cyclopentyloxy)-4-methoxy-phenyl]pyrrolidinone in 20 ml of anhydrous DMF. After stirring 45 minutes at room temperature, (832 mg, 3.63 mmol, 1.0 eq) methyl-3-bromomethylbenzoate was added. After 60 hours at room temperature, the reaction mixture was diluted with 200 ml H_2O and extracted with 200 ml of ethyl acetate. The ethyl acetate extract was washed twice with H_2O, once with brine, dried over Na_2SO_4, and concentrated in vacuo to yield a light yellow oil. Silica gel chromatography eluting with 10%, then 20% ethyl acetate-CH_2Cl_2 yielded 0.33 g, 21%, of a clear oil.

A mixture (0.33 g, 0.78 mmol, 1.0 eq) of the above methyl ester in 8.0 ml of methanol and 2.0 ml of 1N NaOH was heated to reflux for 3 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, diluted with H_2O, acidified to pH 4.5, and extracted with 2 x 200 ml ethyl acetate. The ethyl acetate extracts were combined, washed once with brine, dried over Na_2SO_4, and concentrated to give 300 mg of a white foamy solid. Recrystallization from ethyl acetate-hexane yielded 271 mg, 85%, of white crystals. M.P.: 110-113°C.

EXAMPLE 32

3-[2-[3-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-methenyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one

Pyrrolidine (470 μl, 5.61 mmol, 1.0 eq) was added to a room temperature solution of (1.00 g, 5.61 mmol, 1.0 eq) 6-methoxychromanone and (1.38 g, 5.61 mmol, 1.0 eq) of 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxy benzaldehyde in 25 ml of methanol. After stirring 18 hours at room temperature, the reaction mixture was filtered, and the filtrant washed with methanol twice to yield 1.76 g, 77%, of a yellow powder. M.P.: 82-85°C. Elemental Analysis Calc'd for $C_{25}H_{26}O_5$: Calc'd: C, 73.86; H, 6.45. Found: C, 73.85; H, 6.33.

EXAMPLE 33

3-[2-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-methyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one

A mixture of (1.40 g, 3.44 mmol, 1.0 eq) 3-[2-[3-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methenyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one and 600 mg of 10% Pd/C in 15 ml ethyl acetate and 15 ml tetrahydrofuran was placed on a Parr

Hydrogenator and shaken under 40 psi H_2 at room temperature for 2 hours. The reaction mixture was filtered through celite, and concentrated in vacuo to yield 1.78 g of a pale yellow oil. Silica gel chromatography eluting with CH_2Cl_2 afforded 963 mg, 68%, of a clear oil. High Resolution Mass Spectra: Calc'd: 408.1937. Found: 408.1937.

EXAMPLE 34

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-methyl]-3,4-dihydro-6-methoxy-2H-1-benzopyran-4-ol

Sodium borohydride (59 mg, 1.57 mmol, 0.8 eq) was added to a -50°C solution of (800 mg, 1.96 mmol, 1.0 eq) 3-[2-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-ethyl]-2,3-dihydro-6-methoxy-4H-1-benzopyran-4-one and (730 mg, 1.96 mmol, 1.0 eq) $CeCl_3 \cdot 7H_2O$ in 20 ml of methanol and 7 ml of tetrahydrofuran. The reaction mixture was allowed to warm to room temperature over 18 hours. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, washed once with NH_4Cl (aq.), once with H_2O, once with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a silica gel column eluting with 15% ethyl acetate-hexane, to yield 688 mg of a white amorphous foam. Recrystallization from ethyl acetate-hexane yielded 593 mg, 74%, of white crystals. M.P.: 115-117°C. Elemental Analysis Calc'd for $C_{25}H_{30}O_5$: Calc'd: C, 73.14; H, 7.37. Found: C, 73.35; H, 7.39.

EXAMPLE 35

2-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-*α*-hydroxy-methyl]-4-(phenylmethyl)-2H-1,4-benzothiazin-3(4H)-one

A solution of (1.04 g, 4.06 mmol, 1.0 eq) 4-(phenylmethyl)-2H-1,4-benzothiazin-3-(4H)-one in 10 ml of dry dimethylformamide was added dropwise to a 0°C suspension of (179 mg, 4.47 mmol, 1.1 eq) NaH (60% oil dispersion) in 5 ml of anhydrous dimethylformamide. After stirring at 0°C for 30 minutes, a solution of (1.00 g, 4.06 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde in 10 ml of dry dimethylformamide was added dropwise. The reaction mixture was allowed to come to room temperature over 18 hours, then it was poured into 1L of H_2O, acidified to pH 1, and the resulting precipitate filtered and dried to yield 2 g of a yellow solid. Silica gel chromatography eluting with 2.5% CH_3OH/CH_2Cl_2 followed by recrystallization from ether-hexane yielded 440 mg, 22%, of yellow crystals. M.P.: 159-161°C. Elemental Analysis Calc'd for $C_{30}H_{31}NO_4S$: Calc'd: C, 71.83; H, 6.23; N, 2.79. Found: C, 71.89; H, 6.43; N, 2.81.

EXAMPLE 36

2-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-methylene]-4-(phenylmethyl)-2H-1,4-benzothiazin-3(4H)-one

To a stirred solution of (87 μl, 1.24 mmol, 2.0 eq) dry dimethylsulfoxide in 3 ml of dry CH_2Cl_2 at -65°C was added (0.46 ml, 0.927 mmol, 1.5 eq) of 2.0M oxalyl chloride in CH_2Cl_2. The mixture was stirred at ca. -60°C for 15 minutes, then a solution of (310 mg, 0.618 mmol, 1.0 eq) 2-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]hydroxy-methyl]-4-(phenylmethyl)-2H-1,4-benzothiazin-3(4H)-one in 10 ml dry CH_2Cl_2 was added dropwise at -65°C. The mixture was allowed to warm to -30°C over 1 hour, then cooled to -78°C and (0.43 ml, 3.09 mmol, 5.0 eq) triethylamine was added to the mixture. The mixture was stirred at room temperature for 1 hour then diluted with 400 ml ethyl acetate, washed twice with H_2O, once with brine, dried over $MgSO_4$, and concentrated to give 0.3 g of an oil. Silica gel chromatography eluting with 10% ethyl acetate-hexane gave 120 mg of a yellow oil, which was recrystallized from ether-hexane to yield 55 mg, 18%, of a yellow solid. M.P.: 135-137°C. Elemental Analysis Calc'd for $C_{30}H_{29}NO_3S$: Calc'd: C, 74.51; H, 6.04; N, 2.90. Found: C, 74.53; H, 5.48; N, 2.88.

EXAMPLE 37

6-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-3(2H)-pyridazinone

A mixture of 3-Exo-(±)-norbornyloxy-4-methoxyacetophenone (0.88 g, 3.38 mmol, 1.0 eq) and (0.30 g, 3.29 mmol, 0.95 eq) glyoxylic acid monohydrate was heated to 120°C for 2.2 hours. The light yellow melt was cooled to 60°C and 2.0 ml of H_2O was added. Dissolution was brought on by addition of 25 drops of concentrated NH_4OH. Hydrazine monohydrate (0.163 g, 3.29 mmol, 0.95 eq) was added and the reaction mixture heated to reflux for 2 hours. The reaction mixture was cooled to room temperature, 5 ml of H_2O was added to it, and the mixture stirred for 60 hours at room temperature. The resulting suspension was filtered, washed with H_2O and air dried to yield 0.87 g of a creamy yellow solid. Silica gel chromatography eluting with 5% CH_3OH-CH_2Cl_2, followed by recrystallization from isopropanol-hexane gave 0.50 g, 49%, of off-white crystals. M.P.: 188-189°C. Elemental Analysis Calc'd for $C_{18}H_{20}N_2O_3$: Calc'd: C, 69.21; H, 6.45; N, 8.95. Found: C, 68.92; H, 6.42; N, 8.88.

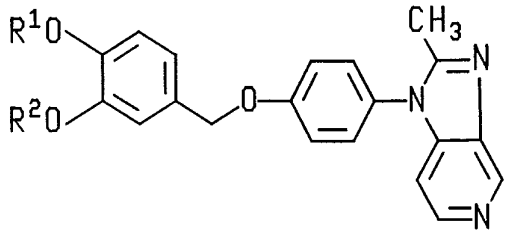
EXAMPLE 38

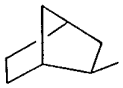
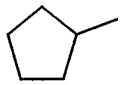
1-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy)-4-(difluoromethoxy)-phenyl]methoxy]phenyl]-2-methyl-1H-imidazo[4,5-c]pyridine

Diethylazodicarboxylate (59 μl, 0.380 mmol, 1.2 eq) was added to a room temperature mixture of (90 mg, 0.317 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-trifluoromethoxybenzaldehyde, (78 mg, 0.348 mmol, 1.1 eq) 4-(2-methyl-1H-imidazo[4.5-c]pyrimidin-3-yl)phenol and (91 mg, 0.348 mmol, 1.1 eq) triphenylphosphine in 5 ml dry tetrahydrofuran. After stirring 18 hours at room temperature, the reaction mixture was diluted with 200 ml of ethyl acetate and washed once with 1N NaOH, once with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 0.2 g of an oil. Flash chromatography on silica gel eluting with 5% CH_3OH/CH_2Cl_2 gave 85 mg of an oil, which was crystallized from ether/hexane to give 69 mg, 45%, of white crystals. M.P.: 140-141°C. Elemental Analysis Calc'd for $C_{28}H_{27}F_2N_3O_3$: Calc'd: C, 68.42; H, 5.54; N, 8.55. Found: C, 68.56; H, 5.38; N, 8.53.

EXAMPLES 39-40

Reaction of the appropriate catechol with 4-(2-methyl-1H-imidazo[4,5-c]pyrimidin-3-yl)phenol, analogous to the procedure of Example 38, yielded the following compounds:



Ex.#	R^1	R^2	M.P.°C	Analysis					
				Calculated (%)			Found (%)		
				C	H	N	C	H	N
39	CH_3		122-4°	75.47	6.56	9.43	73.56	6.27	9.03
40	CH_3		151-3°	72.71	6.34	9.78	72.05	6.35	9.16

EXAMPLE 41

1-[4-[2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-ethenylphenyl]-2-methyl-1H-imidazo[4,5-c]pyridine

To a stirred suspension of (1.74 g, 3.13 mmol, 1.2 eq) [[3-(cyclopentyloxy)-4-methoxyphenyl]methyl]triphenylphosphonium bromide in 20 ml dry tetrahydrofuran at -50°C was added (1.1 ml, 2.78 mmol, 1.1 eq) of 2.5M n-BuLi. The mixture was warmed to 0°C over 1 hour, cooled to -78°C, and a solution of (600 mg, 2.53 mmol, 1.0 eq) 4-(2-methyl-1H-imidazo[4,5-c]pyridin-1-yl)benzaldehyde in 20 ml dry tetrahydrofuran was added dropwise over 10 minutes. The reaction mixture was allowed to warm to room temperature over 18 hours then was quenched with 10 ml saturated NH_4Cl solution. The mixture was poured into 200 ml of H_2O and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with H_2O, once with brine, dried over $MgSO_4$, and concentrated to give 2 g of an oil. Flash chromatography eluting with 65% acetone-hexane gave 403 mg of crude product, which was recrystallized from ether-hexane to yield 305 mg, 36%, of the cis product. The trans product was isolated from the chromatography yielding 476 mg, and crystallized from isopropylether to give 415 mg, 39%. Cis-product M.P.: 123-125°C. Trans-Product M.P.: 156-158°C. Elemental Analysis of the cis-product: Calc'd for $C_{27}H_{27}N_3O_2$: Calc'd: C, 76.21; H, 6.40; N, 9.87. Found: C, 76.14; H, 6.34; N, 9.71.

EXAMPLE 42

1-[4-[2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-ethyl]phenyl]-2-methyl-1H-imidazo[4,5-c]pyridine

A cis and trans mixture of 1-[4-[2-[3-(cyclopentyloxy)-4-methoxyphenyl]-ethenyl]phenyl]-2-methyl-1H-imidazo[4,5-c]pyridine (300 mg, 0.705 mmol 1.0 eq) and 300 mg of 10% Pd/C in 10 ml of tetrahydrofuran and 10 ml of methanol was placed on a Parr hydrogenation apparatus and shaken under 50 psi H_2 at room temperature for 6 hours. The reaction mixture was filtered through celite, concentrated, and chromatographed on a silica gel column eluting with 5% CH_3OH-CH_2Cl_2 to give 230 mg of clear oil. Recrystallization from ether-hexane gave 239 mg, 79%, of white crystals. M.P.: 123-125°C. Elemental Analysis Calc'd for $C_{27}H_{29}N_3O_2$: Calc'd: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.83; H, 6.74; N, 9.65.

EXAMPLE 43

Methyl 1-[4-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxyphenyl]-2-butyl-1H-benzimidazole-5-carboxylate

Diethylazodicarboxylate (201 μL, 1.28 mmol, 1.3 eq) was added to a mixture of (320 mg, 0.986 mmol, 1.0 eq) methyl 2-butyl-1-(4-hydroxyphenyl)-1H-benzimidazole-5-carboxylate, (269 mg, 1.08 mmol, 1.1 eq) (±)-3-exo-norbornyloxy-4-methoxybenzyl alcohol and (310 mg, 1.18 mmol, 1.2 eq) of triphenylphosphine in 10 ml of dry tetrahydrofuran at room temperature. The reaction mixture was stirred at room temperature for 18 hours, diluted with 300 ml of ethyl acetate and washed twice with 1N NaOH, once with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 0.7 g of an oil. Silica gel chromatography eluting with 35% ethyl acetate/hexane gave 298 mg, 54%, of an off-white foam. Mass Spectra: Calc'd for $C_{34}H_{38}N_2O_5$: 554.7. Found: 554.

EXAMPLE 44

1-[4-[[3-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]phenyl-2-butyl-1H-benzimidazole-5-carboxlyic acid

Reaction of (260 mg, 0.469 mmol, 1.0 eq) methyl 1-[4-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methoxy]phenyl]-2-butyl-1H-benzimidazole-5-carboxylate, (2.3 ml, 2.3 mmol, 5.0 eq) substantially according to the procedure of Example 4 yielded the title compound, 178 mg, 70%, as a white solid. M.P.: 209-211°C. Elemental Analysis Calc'd for $C_{33}H_{36}N_2O_5$: Calc'd: C, 73.31; H, 6.71; N, 5.18. Found: C, 72.92; H, 6.74; N, 4.94.

EXAMPLE 45

1-[4-[[3-(Bicyclo[2.2.1]-hept-2-yloxy-4-methoxyphenyl]-methoxy]phenyl]-2-butyl-1H-imidazo[4,5-c]pyridine

Diethylazodicarboxylate (441 μl, 2.56 mmol, 1.2 eq) was added to a mixture of (570 mg, 2.13 mmol, 1.0 eq) 4-[3H-imidazo[4,5-b]-2-butyl pyridine]phenol, (582 mg, 2.35 mmol, 1.1 eq) (±)-3-exo-norbornyloxy-4-methoxybenzyl alcohol and (616 mg, 2.35 mmol, 1.1 eq) of triphenylphosphine in 25 ml tetrahydrofuran at room temperature. After stirring at room temperature for 60 hours, the reaction mixture was diluted with 400 ml ethyl acetate, washed once with 1N NaOH, once with H_2O, once with brine, dried over $MgSO_4$, and concentrated to give 1 g of an oil. Silica gel chromatography eluting with 5% CH_3OH/CH_2Cl_2, followed by recrystallization from ether/hexane gave 328

mg, 31%, of a solid. M.P.: 123-125°C. Elemental Analysis Calc'd for $C_{31}H_{35}N_3O_3$: Calc'd: C, 74.97; H, 6.90; N, 8.46. Found: C, 74.63; H, 7.12; N, 8.29.

EXAMPLE 46

1-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy]-
4-difluoromethoxyphenyl]methoxy]phenyl]-
2-butyl-2H-imidazo[4,5-c]pyridine

Reaction of (±)-3-exo-norborynyloxy-4-difluoromethyloxybenzyl alcohol with 4-3H-imidazo[4,5-b]-2-butylpyridine phenol, analogous to the procedure of Example 45, yielded the above-identified compound. M.P.: 129-131°C. Elemental Analysis Calc'd for $C_{31}H_{33}F_2N_3O_3$: Calc'd: C, 69.78; H, 6.23; N, 7.82. Found: C, 69.66; H, 6.13; N, 7.82.

EXAMPLE 47

3-[4-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-methoxyphenyl]methoxy]phenyl]-
2-butyl-3H-imidazo[4,5-b]pyridine

Diethylazodicarboxylate (365 μl, 2.11 mmol, 1.2 eq) was added to a mixture of (470 mg, 1.76 mmol, 1.0 eq) 4-(2-methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenol, (480 mg, 1.93 mmol, 1.1 eq) (±)-3-exo-norbornyloxy-4-methoxybenzyl alcohol, and (506 mg, 1.93 mmol, 1.0 eq) triphenylphosphine in 20 ml of dry tetrahydrofuran. After stirring at room temperature for 60 hours, the reaction mixture was diluted with 400 ml of ethyl acetate, washed twice with 1N NaOH, once with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 0.8 g of an oil. Silica gel chromatography eluting with 60% ethyl acetate/hexane, followed by recrystallization from ether/hexane gave 195 mg, 24%, of tan crystals. M.P.: 130-132°C. Elemental Analysis Calc'd for $C_{31}H_{35}N_3O_3$: Calc'd: C, 74.82; H, 7.09; N, 8.44. Found: C, 74.44; H, 7.23; N, 8.30.

EXAMPLE 48

3-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy]-
4-methoxyphenyl]methoxy]phenyl-
2-methyl-3H-imidazo[4,5-b]pyridine

Reaction of 2-methyl-3-(4-hydroxyphenyl)-4-azabenzimidazole with (±)-3-exo-norbornyloxy-4-methoxybenzyl alcohol, analogous to the procedure of Example 47, yielded the title compound. M.P.: 72-75°C. Elemental Analysis Calc'd for $C_{28}H_{29}N_3O_3$: Calc'd: C, 73.82; H, 6.42; N, 9.22. Found: C, 73.12; H, 6.34; N, 8.86.

EXAMPLE 49

1-[4-[[3-Bicyclo[2.2.1]hept-2-yloxy]-4-methoxy-phenyl]methoxy] phenyl-2-butyl-1H-benzimidazole

Diethylazodicarboxylate (90 μl, 0.580 mmol, 1.2 eq) was added to a mixture of (120 mg, 0.483 mmol, 1.0 eq) 2-butyl-3-(4-hydroxyphenyl)benzimidazole, (126 mg, 0.507 mmol, 1.05 eq) (±)-3-exo-norbornyloxy-4-methoxybenzyl alcohol, and (139 mg, 0.531 mmol, 1.1 eq) triphenylphosphine in 10 ml anhydrous tetrahydrofuran. After 18 hours at room temperature, the reaction mixture was diluted with 200 ml of ethyl acetate, washed twice with 1N NaOH, once with H_2O, once with brine, dried over $MgSO_4$, concentrated in vacuo to give 0.2 g of an oil. Silica gel chromatography eluting with 40% ethyl acetate/hexane followed by recrystallization from ether/hexane gave 66 mg, 28%, white crystals. M.P.: 134-136°C. Elemental Analysis Calc'd for $C_{32}H_{36}N_2O_3$: Calc'd: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.08; H, 6.94; N, 5.43.

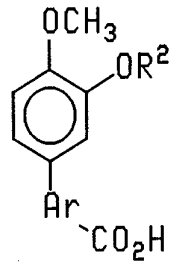
EXAMPLE 50

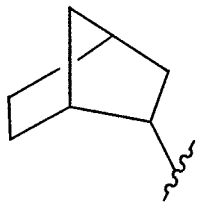
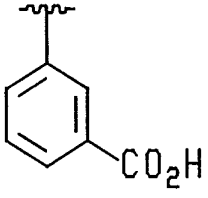
4-[4-Methoxy-3-(4-phenylbutyloxy)phenyl]benzoic Acid

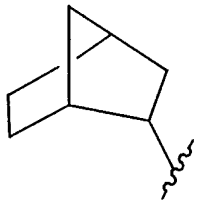
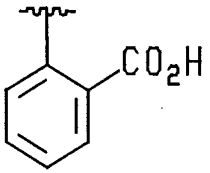
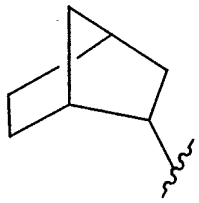
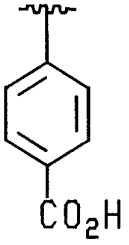
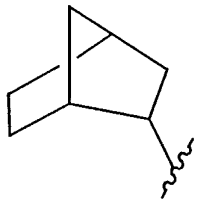
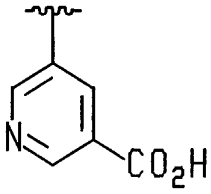
To a solution of (2.9 g, 8.65 mmol, 1.0 eq) 1-methoxy-2-(4-phenyl-1-butoxy)-4-bromobenzene in 30 ml of dry THF at -78°C was added (3.81 ml, 9.52 mmol, 1.1 eq) 2.5M n-BuLi. After stirring 15 minutes at -78°C, (10.4 ml, 10.4 mmol, 1.2 eq) 1.0M $ZnCl_2$ in ether was added and the mixture allowed to warm to room temperature over 35 minutes. Tetrakis(triphenylphosphine)palladium(0) (500 mg, 0.43 mmol, 0.05 eq) and (2.27 g, 8.65 mmol, 1.0 eq) methyl-4-iodobenzoate were added to the reaction and the mixture allowed to stir at room temperature for 2.5 hours. The reaction mixture was concentrated in vacuo, costripped with $CHCl_3$, and chromatographed on a silica gel column eluting with ethyl acetate-hexane (0-10%) to afford 2.61 g, 76%, of a yellow solid. Hydrolysis of the ester according to the method of Example 4 gave the title compound, M.P.: 178-179°C. Elemental analysis calculated for $C_{24}H_{24}O_4$: C, 76.56; H, 6.43. Found: C, 76.06; H, 5.92.

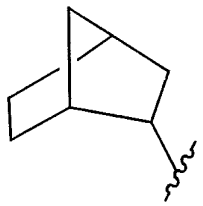
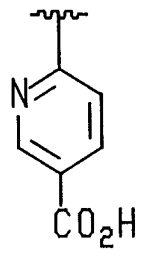
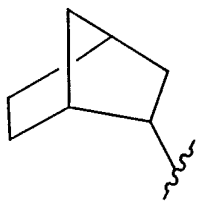
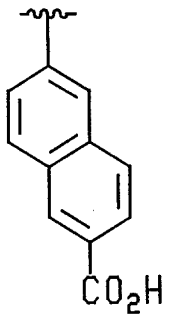
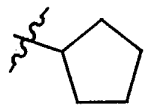
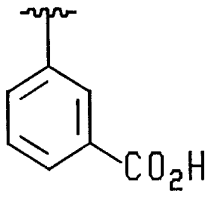
EXAMPLES 51-72

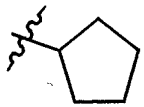
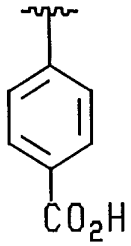
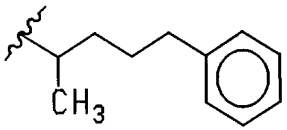
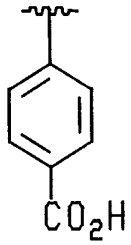
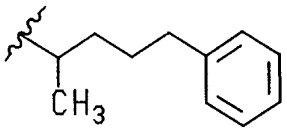
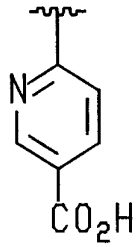
Reaction of the appropriate bromocatechol, with the required halo aromatic ester of the formula X-Ar-C-OR^4 (O) analogous to the procedure of Example 50, followed by hydrolysis substantially according to the procedure of Example 4 yielded the following compounds of the general formula:

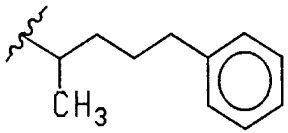
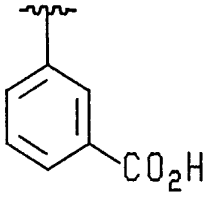
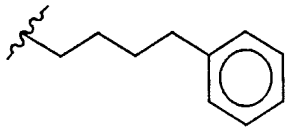
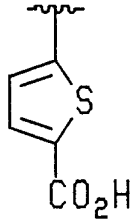
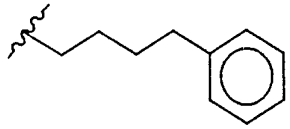
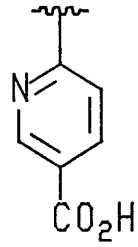


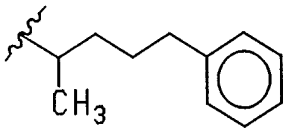
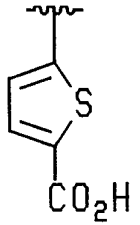
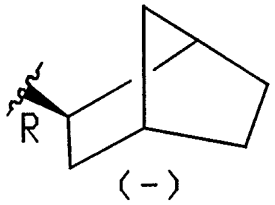
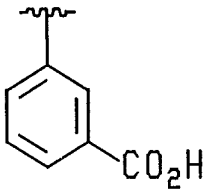
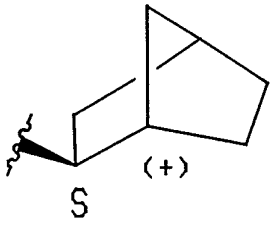
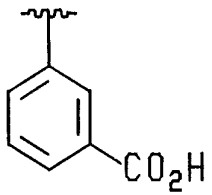
Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
51			128-9°	74.54	6.55	--	74.86	6.82	--

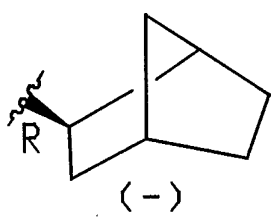
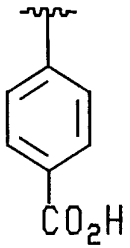
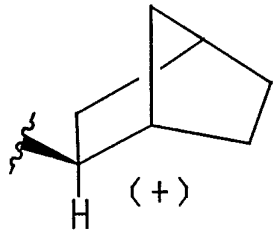
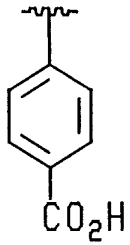
Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
52			66-8°	74.54	6.55	--	75.10	6.20	--
53			230-2°	74.54	6.55	--	74.36	6.20	--
54			236-8°	70.78	6.24	4.13	69.95	6.09	4.17

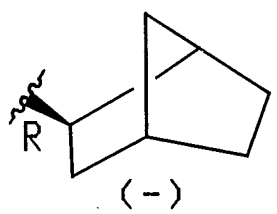
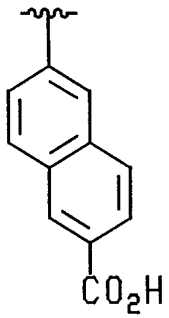
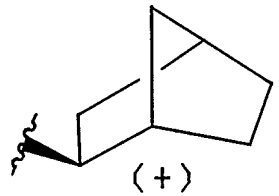
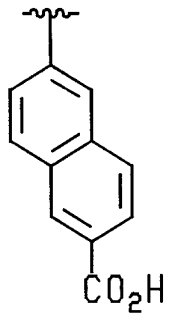
Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
55			221-3°	70.78	6.24	4.13	70.60	6.08	4.02
56			242-5°	77.30	6.23	--	76.04	5.91	--
57			149-51°	73.05	6.47	--	72.91	6.56	--

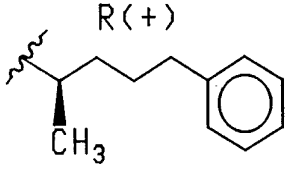
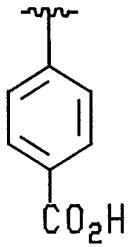
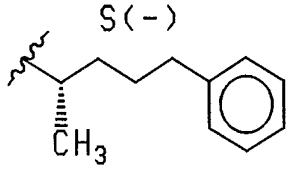
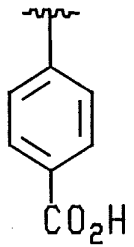
Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
58			230-32°	73.05	6.47	--	73.16	6.51	--
59			136-8°	76.90	6.71	--	76.95	6.48	--
60			148-50°	73.63	6.45	3.58	73.45	6.39	3.65

Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
61			72-4°	76.90	6.71	--	77.08	6.49	--
62			118-9°	69.07	5.81	--	68.75	5.61	--
63			188-9°	73.18	6.15	3.71	72.93	6.11	3.69

Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
64			122-4°	--	--	--	--	--	--
65			oil	--	--	--	--	--	--
66			oil	--	--	--	--	--	--

Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
67			234-6°	74.53	6.55	--	74.49	6.24	--
68			234-6°	74.53	6.55	--	74.53	6.17	--

Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
69	 (-)		242-4°	77.30	6.23	--	77.28	6.25	--
70	 (+)		243-5°	--	--	--	--	--	--

Ex.#	R^2	$ArCO_2H$	M.P. °C	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
71			159-60°	76.90	6.71	--	76.82	6.58	--
72			159-60°	76.90	6.71	--	76.87	6.69	--

EXAMPLE 73

2-[(4-Methoxy-4'-nitro[1,1'-biphenyl]-3-yl)oxy]bicyclo[2.2.1]heptane

To a stirred solution of (2 g, 6.73 mmol, 1.0 eq) (±)-1-methoxy-2-exo-norbornyloxy-4-bromobenzene in 50 ml of dry THF at -78°C was added 2.96 ml (7.40 mmol, 1.1 eq) 2.5M n-BuLi. After about 45 minutes at -78°C, (8.07 ml, 8.07 mmol, 1.2 eq) 1.0M $ZnCl_2$ in ether was added and the reaction mixture allowed to warm to room temperature over 30 minutes. Pd $(PPh_3)_4$ (389 mg, 0.34 mmol, 0.05 eq) and then (1.67 g, 6.73 mmol, 1.0 eq) 1-nitro-4-iodobenzene were added and the reaction mixture stirred 30 minutes at room temperature. The mixture was concentrated in vacuo and chromatographed on silica gel, eluting with ethyl acetate/hexane (0-8%) to afford 1.32 g, 58%, of a yellow solid. M.P.: 134-135°C.

EXAMPLE 74

4'-Methoxy-3'-(1-methyl-4-phenyl-butoxy)-[1,1'-biphenyl]-4-tetrazole

A solution of (525 mg, 8.07 mmol, 1.2 eq) NaN_3 in 10 ml H_2O was added to a stirred solution of (1.8 ml, 6.70 mmol, 1.0 eq) of Bu_3SnCl in 75 ml of ether. The mixture was stirred 45 minutes at room temperature then the layers were separated and the aqueous layer extracted once with ether. The ether extracts were combined, washed once with brine, dried over $MgSO_4$, and concentrated to yield a clear, colorless oil, used directly in the next reaction.

To a mixture of (2.22 g, 6.7 mmol, 1.7 eq) crude Bu_3SnN_3 in 50 ml dry THF was added a solution (1.5 g, 4.04 mmol, 1.0 eq) of the nitrile (see Preparation 39) in 50 ml dry THF. The reaction mixture was heated to reflux and stirred for 4 days. The mixture was cooled, concentrated in vacuo, and chromatographed on silica gel eluting with hexane-ethyl acetate-acetic acid (75:24:1), then recrystallized from ethyl acetate-hexane to afford 565 mg, 34%, of an off white solid. M.P.: 139-140°C.

EXAMPLE 75

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenoxy] benzoic acid

To a solution (1 g, 4.27 mmol, 1.0 eq) of 3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxy phenol and (0.63 ml, 4.27 mmol, 1.0 eq) ethyl-4-fluorobenzoate in 45 ml of dimethylacetamide was added (708 mg, 5.12 mmol, 1.2 eq) K_2CO_3. After heating to reflux for 18 hours, the reaction mixture was cooled to room temperature, poured into 75 ml of H_2O and extracted twice with ethyl acetate. The ethyl acetate extracts were

combined, washed once with brine, dried over $MgSO_4$, and concentrated to give a dark brown oil. Chromatography on silica gel eluting with ethyl acetate-hexane (0-15%) gave 590 mg, 26%, of a light yellow oil.

A mixture of (750 mg, 1.96 mmol, 1.0 eq) of the above ester and 10 ml of 2N NaOH in 20 ml of ethanol was heated to reflux for 2 hours. The mixture was diluted with 50 ml of H_2O, acidified to pH 4 and extracted twice with ethyl acetate. The combined organic layers were washed once with brine, dried over Na_2SO_4, and concentrated to give an off-white solid. Recrystallization from ethyl acetate/hexane afforded 425 mg, 61%, of a white crystalline solid. M.P.: 116-117°C. Elemental Analysis Calc'd for $C_{21}H_{22}O_5$: Calc'd: C, 71.16; H, 6.27. Found: C, 70.98; H, 6.18.

EXAMPLE 76

N-[3'-(Bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-yl]-1,1,1-trifluoromethanesulfonamide
and
N,N-[3'-(Bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy-[1,1'-biphenyl]-4-yl]-bis(1,1,1-trifluorodimethanesulfonamide)

To a mixture of (450 mg, 1.45 mmol, 1.0 eq) of 3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-amino and (0.24 ml, 1.74 mmol, 1.2 eq) triethylamine in 6 ml of CH_2Cl_2 at -78°C was added 0.27 ml (1.60 mmol, 1.0 eq) of triflic anhydride dropwise. The reaction mixture was stirred 10 minutes at -78°C and then 1.5 hours at 0°C. The mixture was concentrated in vacuo, costripped twice with $CHCl_3$ then chromatographed on silica gel eluting with ethyl acetate-hexane (10% → 30%) to afford 187 mg, 22%, of N,N-[3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-yl]-1,1,1-trifluorodimethanesulfonamide and 70 mg, 11%, of N-[3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-yl]-1,1,1-trifluoromethanesulfonamide. M.P. of the dimethanesulfonamide: 146-147°C. M.P. of the methanesulfonamide: 138-139°C. Dimethanesulfonamide Elemental Analysis Calc'd for $C_{22}H_{21}NO_6S_2F_6$: Calc'd: C, 46.07; H, 3.70; N, 2.44. Found: C, 46.21; H, 3.63; N, 2.51.

EXAMPLE 77

N-(3'-Bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy-[1,1'-biphenyl]-4-ylmethanesulfonamide

To a stirred solution of (525 mg, 1.70 mmol, 1.0 eq) 3'-(bicyclo[2.2.1]hept-2-yloxy)-4'-methoxy[1,1'-biphenyl]-4-amino in 10 ml dry CH_2Cl_2 at 0°C was added 0.28 ml of triethylamine (2.03 mmol, 1.2 eq), followed by 355 mg (2.03 mmol, 1.2 eq) methanesulfonic anhydride. The mixture was stirred at 0°C for 10 minutes, then at

room temperature for 1 hour, at which point an additional 200 mg (1.1 mmol, 0.7 eq) of methane sulfonic anhydride was added. After stirring an additional 30 minutes at room temperature, the reaction mixture was concentrated in vacuo, costripped twice with $CHCl_3$, and chromatographed on silica gel eluting with ethyl acetate-hexane (10-35%) to yield 700 mg of compound. Recrystallization from ethyl acetate/hexane afforded 650 mg, 98%, of crystals. M.P.: 151-153°C. Elemental Analysis Calc'd for $C_{21}H_{25}NO_4S$: Calc'd: C, 65.08; H, 6.51; N, 3.61. Found: C, 64.92; H, 6.21; N, 3.53.

EXAMPLE 78

Methyl 1-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-1H-indole-3-carboxylate

A mixture of (1.0 g, 5.71 mmol, 1.0 eq) 3-carbomethoxy indole, (2.21 g, 7.42 mmol, 1.3 eq) (±)-1-methoxy-2-exo-norbornyloxy-4-bromobenzene (30.7 mg, 0.107 mmol, 0.2 eq) cuprous bromide, and (866 mg, 6.27 mmol, 1.1 eq) potassium carbonate in 15 ml of 1-methyl-2-pyrrolidinone was heated to 150°C for 24 hours. The reaction mixture was cooled, diluted with 350 ml of ethyl acetate and 350 ml of H_2O, and the layers separated. The aqueous layer was extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H_2O, once with brine, dried over Na_2SO_4 and concentrated in vacuo to give a light brown oil. Silica gel chromatography eluting with 20% ethyl acetate/hexane gave 1.05 g, 47%, of a white foamy solid. M.P.: 120-122°C. Elemental Analysis Calc'd for $C_{24}H_{25}NO_4$: Calc'd: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.70; H, 6.37; N, 3.59.

EXAMPLE 79

1-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxy]-1H-indole-3-carboxylic acid

A mixture of (0.85 g, 2.17 mmol, 1.0 eq) of methyl 1-[3-(bicyclo[2.2.1]-hept-2-yloxy)-4-methoxyphenyl]-1H-indole-3-carboxylic acid and 20 ml of 1N NaOH in 50 ml of CH_3OH was heated to reflux for 18 hours. The reaction mixture was cooled, diluted with 150 ml of H_2O, and acidified to pH 1. The white precipitate that formed was filtered, washed with H_2O and air dried to yield 0.68 g of a white solid. Recrystallization from ethyl acetate/hexane afforded 565 mg, 69%, of white powder. M.P.: 203-205°C. Elemental Analysis Calc'd for $C_{23}H_{23}NO_4$: Calc'd: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.01; H, 6.23; N, 3.66.

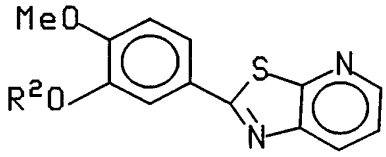
EXAMPLE 80

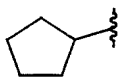
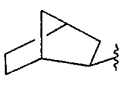
2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-fluorobenzothiazole

A mixture of (440 mg, 2 mmoles) 4-methoxy-3-cyclopentyloxy benzaldehyde and (400 mg, 2.1 mmoles) 2-mercapto-5-fluoroaniline hydrochloride was heated on a steam bath for 15 minutes. The resulting thick orange oil was cooled and dissolved in 5 ml of 10% $FeCl_3$ in methanol and allowed to stir overnight. The reaction was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried and evaporated to give 760 mg of crude product which was purified on silica gel with CH_2Cl_2 to give 500 mg of product. Recrystallization from isopropanol gave 140 mg of product. M.P.: 96-97°C. Elemental Analysis Calc'd for $C_{19}H_{18}O_2NSF$: Calc'd: C, 66.45; H, 5.28; N, 4.08. Found: C, 66.44; H, 5.13; N, 4.06.

EXAMPLES 81-82

Reaction of the appropriate aldehyde with 2-mercapto-3-aminopyridine, analogous to the procedure of Example 80, yielded the following compounds of the formula



Ex.#	R^2	M.P. °C	Analysis					
			Calculated %			Found %		
			C	H	N	C	H	N
81		118-120°	66.23	5.56	8.58	66.41	5.71	8.42
82		110-111°	--	--	--	--	--	--

EXAMPLE 83

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
1H-benzimidazole-5-carboxylic acid

A mixture of (800 mg, 5.3 mmoles) cyclopentyl bromide, (1.6 g, 5.3 mmoles) methyl 1-(3-hydroxy-4-methoxyphenyl)-1H-benzimidazole-5-carboxylate and 251 mg of 60% sodium hydride in 10 ml of dimethylformamide was stirred at 100° for 30 minutes. The reaction was cooled, poured onto H_2O and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 2 g of crude product. Purification on silica gel with CH_2Cl_2 gave 1.1 g of methyl 1-(3-cyclopentyl-4-methoxyphenyl)-1H-benzimidazole-5-carboxylate. M.P.: 129-131°.

A solution of 500 mg of the above methyl ester in 20 ml of methanol containing 5 ml of 1N NaOH was heated on a steam bath for 30 minutes. The reaction was cooled and the methanol removed in vacuo. The residue was acidified with 1N HCl and the resulting solid was filtered and recrystallized from methanol to give 198 mg of product. M.P. >250°C.

EXAMPLE 84

2-[3-(Cyclopentyloxy)-4-methoxy-
phenyl]oxazolo[4,5-b]pyridine

A solution of 500 mg of 2-N[3-(cyclopentyloxy)-4-methoxyphenylcarbonyl]amino-3-hydroxypyridine in 15 ml of $POCl_3$ was heated at reflux for 20 hours. Excess $POCl_3$ was evaporated and the crude product was purified by chromatography on silica gel with CH_2Cl_2/methanol to give 165 mg of the title product. M.P.: 108-109°C.

EXAMPLE 85

2-[3-(Cyclopentyloxy)-4-methoxy-
phenyl]oxazolo[5,4b]pyridine

Reaction of 4-methoxy-3-cyclopentyloxybenzoic acid chloride with 2-hydroxy-3-amino pyridine, analogous to the procedure of Example 84 yielded the title compound. M.P.: 141-142°C. Elemental Analysis Calc'd for $C_{18}H_{18}N_2O_3$: Calc'd: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.51; H, 5.76; N, 8.90.

EXAMPLE 86

2-(3-Cyclopentyloxy-4-methoxyphenyl)thiazole

A solution of 130 mg of 3-cyclopentyloxy-4-methoxybenzthioamide and 100 mg of chloroacetaldehyde in 15 ml of ethanol was heated at reflux for 6 hours. The volatiles were evaporated and the residue purified on silica gel with CH_2Cl_2 to give 90 mg of product. M.P.: 72-75°C.

EXAMPLE 87

2-(3-Cyclopentyloxy-4-methoxy phenyl)-5-thiazolecarboxylic acid

Reaction of 3-methoxy-4-cyclopentyloxybenzthioamide with chlorocarboethoxy-acetaldehyde, analogous to the procedure of Example 86, yielded the ethyl ester of the title compound, which was hydrolyzed under basic conditions to yield the title compound. M.P.: 170-171°C.

EXAMPLE 88

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-thiazolacetic acid

A solution of (660 mg, 6.5 mmoles) of 4-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-methylthiazole in THF was added dropwise to a solution of lithium diisopropylamide in THF at -78°C. After 1 hour at -78°C dry CO_2 was bubbled into the reaction for 2 minutes. The reaction was allowed to warm to room temperature, acidified with dilute HCl and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 420 mg product. Recrystallization from hexane 290 mg product. M.P.: 190-191°C.

EXAMPLE 89

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl-2-thiazolecarboxylic acid

Reaction of the chloroketone of Preparation 43 with ethyl thiooxanate, analogous to the procedure of Example 88, yielded the ethyl ester of the title compound which was then hydrolyzed according to the procedure of Example 8 to give the title compound. M.P.: 112-113°C.

EXAMPLE 90

4-[3-(Bicyclo[2.2.1]hept-2-yloxy-4-methoxyphenyl]-2-thiazolamine

Reactions of the chloroketone of Preparation 43 with thiourea, analogous to the procedure of Example 88, yielded the title compound. M.P.: 168-178°C.

EXAMPLE 91

1-[3-(Cyclopentyloxy)-4-methoxy-phenyl]-1H-imidazo[4,5-c]pyridine

A solution of 2.05 g of 1-(3-hydroxy-4-methoxyphenyl)-1H-imidazo[4,5-c]pyridine, 2.5 g of cyclopentylbromide and 665 mg of NaH in 20 ml of DMF was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl

acetate, dried to give 1.4 g of crude product. Recrystallization from CH_2Cl_2 gave 574 mg product. M.P.: 66-68°C.

EXAMPLE 92

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
2-methyl-1H-imidazo[4,5-c]pyridine

Reaction of 3-hydroxy-4-methoxy-N-[4-(3-amino)pyridinyl]aniline with acetic acid, analogous to the procedure of Preparation 44, and subsequent reactions with cyclopentylbromide analogous to the procedure of Example 91, yielded the title compound. M.P.: 144-145°C.

EXAMPLE 93

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-
2-ethyl-1H-imidazo[4,5-c]pyridine

Reaction of 3-hydroxy-4-methoxy-N-[4-(3-amino)pyridinyl]aniline with propionic acid analogous to the procedure of Preparation 44, and subsequent reaction with cyclopentylbromide, analogous to the procedure of Example 91, yielded the title compound.

EXAMPLE 94

2-[3-[2-Indoxy]-4-methoxyphenyl]-1H-imidazo[4,5-b]pyridine

A. Preparation of 3-(2-indoxy)-4-methoxybenzoic acid

To a magnetically stirred solution of 3-(2-indoxy)-4-methoxybenzaldehyde (3.0 g, 11.2 mmoles) in acetone (50 ml) was added 7 ml of 2.67 M solution of Cr_2O_3 in 50% aqueous H_2SO_4. This was exothermic enough to effect a mild reflux of acetone, and no external cooling was necessary. After stirring overnight at ambient temperature, 50 ml of H_2O was added, and the acetone was allowed to evaporate over a steam bath. The crude product was filtered and washed with 1N HCl followed by water. Recrystallization from isopropyl ether gave 1.9 g of off-white crystals. M.P.: 189-191°C.

B. Preparation of 3-(2-indoxy)-4-methoxybenzoyl chloride

A solution of 0.50 g of 3-(2-indoxy)-4-methoxybenzoic acid in 10 ml of thionyl chloride was heated at reflux for 1 hour. Removal of the volatiles under reduced pressure gave a dull pink solid which was immediately used in the next step without purification.

C. Preparation of the title compound

To a magnetically stirred solution of 2,3-diaminopyridine (1.8 mmole) in dry pyridine (15 ml) at 0°C was added dropwise a solution of 3-(2-indoxy)-4-methoxybenzoyl chloride in dry THF (10 ml). After 1 hour the mixture was warmed to ambient temperature and after 16 hours the volatiles were removed under reduced pressure. The residue was suspended in 25 ml of water, filtered, and washed with water to give 0.59 g of a white solid. M.P.: 226-228°C (dec).

The above amide was suspended in 10 ml of phosphorous oxychloride and heated at reflux for 1.5 hours, at which time the reaction mixture was homogeneous. The volatiles were removed under reduced pressure, and the residue was suspended in 25 ml of saturated sodium bicarbonate, filtered, and air-dried. Column chromatography followed by recrystallization from ethanol gave 180 mg of off-white crystals. M.P.: 206-208°C. Elemental analysis calculated for $C_{22}H_{19}O_2N_3$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.01; H, 5.06; N, 11.76.

EXAMPLE 95

2-[3-[2-Indoxy]-4-methoxyphenyl]thiazo[5,4-b]pyridine

A. Preparation of 3-amino-2-thiopyridine

A mixture of 3-amino-2-chloropyridine (25 g, 190 mmoles), sodium hydrogen sulfide (58 g, 780 mmoles) and propylene glycol (75 ml) were heated at reflux for 5 hours. The solvent was removed under reduced pressure, and the resulting residue was dissolved in 300 ml of water and acidified to pH 5 with AcOH. After stirring for 1 hour the mixture was filtered to give 14.3 g of a dark brown solid. Recrystallization from toluene provided dark brown needles. M.P.: 131-132°C.

B. Preparation of the title compound

To a magnetically stirred solution of 3-amino-2-thiopyridine (0.22 g) in dry pyridine (15 ml) at 0°C was added dropwise a solution of 3-(2-indoxy)-4-methoxy-benzoyl chloride (0.50 g) in dry THF (10 ml). After 1 hour the mixture was warmed to ambient temperature and after 16 hours the volatiles were removed under reduced pressure. The residue was suspended in 25 ml of water, filtered, and washed with water to give 0.60 g of a gold solid. M.P.: 252-253°C (dec).

The above amide (0.58 g, 1.5 mmoles) and $POCl_3$ (10 ml) were heated at reflux. After 1.5 hours the mixture was slowly poured into water, cooled, and extracted with ether. The combined organics were dried over $MgSO_4$ and concentrated to give a pale yellow solid. Recrystallization from methanol gave 0.32 g of product as its HCl salt.

The salt was dissolved in methylene chloride and washed with 1N NaOH to give a white solid. Recrystallization from methanol gave 0.25 g of a white solid. M.P.: 159-160°C. Elemental analysis calculated for $C_{22}H_{18}O_2N_2S$: C, 70.57; H, 4.84; N, 7.48. Found: C, 70.46; H, 4.72; N, 7.35.

EXAMPLE 96

2-[3-[2-Indoxy]-4-methoxyphenyl]oxazo[5,4-b]pyridine

A. Preparation of 3-amino-2-pyridone

3-Nitro-2-pyridone (2.0 g, 14 mmoles), 10% Pd/C (0.20 g) and methanol (50 ml) were placed on a Parr shaker under 45 psi of H_2. After 18 hours the mixture was filtered and concentrated to give 1.3 g of a pale pink solid. M.P.: 123-125°C.

B. Preparation of the title compound

To a magnetically stirred solution of 3-amino-2-hydroxypyridine (1.8 mmole) in dry pyridine (15 ml) at 0°C was added dropwise a solution of 3-(2-indoxy)-4-methoxybenzoyl chloride in dry THF (10 ml). After 1 hour the mixture was warmed to ambient temperature and after 16 hours the volatiles were removed under reduced pressure. The residue was suspended in 25 ml of water, filtered, and washed with water to give 0.57 g of a white solid. M.P.: 282-284°C (dec).

The above amide was suspended in 10 ml of phosphorous oxychloride and heated at reflux for 1.5 hours, at which time the reaction mixture was homogeneous. The volatiles were removed under reduced pressure, and the residue was suspended in 25 ml of saturated sodium bicarbonate, filtered, and air-dried. Column chromatography (silica, 1:3 EtOAc/hexane) gave 160 mg of a white solid. M.P.: 193-194°C.

EXAMPLE 97

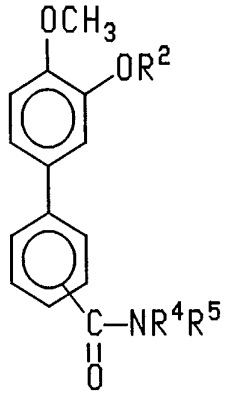
4'-Methoxy-3'-(4-phenylbutoxy)-
(±)[1,1'-biphenyl]-4-carboxamide

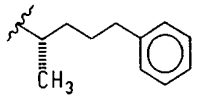
A suspension of (0.522 g, 1.38 mmoles) 4-[4-methoxy-3-(4-phenylbutyl-oxy)phenyl]benzoic acid in dry methylene chloride was treated with excess thionyl chloride (0.505 ml, 6.93 mmoles) and a catalytic amount of anhydrous DMF (3-5 drops). The resulting clear solution was heated to reflux under nitrogen atmosphere for 1 hour. The methylene chloride was removed in vacuo and the resulting light yellow solid residue azeotroped with additional 15 ml of dry methylene chloride. The residue was dissolved in 15 ml of dry CH_2Cl_2, cooled to 0°C (ice bath) and dry anhydrous ammonia gas bubbled directly into the reaction mixture for approximately 5 minutes. This was

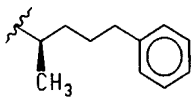
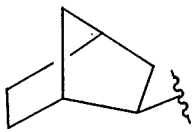
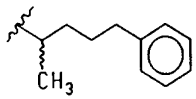
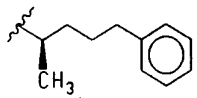
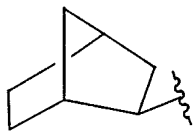
followed by allowing the reaction to stir at 0°C for an additional hour, after which time the reaction mixture was diluted with 500 ml of ethyl acetate and 300 ml of H_2O. The organic layer was separated and washed with 1N HCl (2 x 350 ml), 2N NaOH (2 x 350 ml), water (1 x 300 ml), brine, dried over $MgSO_4$ and evaporated under reduced pressure which yielded a white solid. Recrystallization from ethyl acetate-hexane gave a total of 0.37 grams of white crystals. M.P.: 180-182°C. Elemental Analysis Calc'd for $C_{24}H_{25}O_3N$: Calc'd: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.93; H, 6.71; N, 3.73.

EXAMPLES 98-104

Reaction of the appropriate carboxylic acid with the required amine of the general formula NR_1R_2, analogous to the procedure of Example 97, yielded the following compounds:



Ex.#	R^2	R^4	R^5	Position of Amide	M.P. °C	Analysis					
						Calculated %			Found %		
						C	H	N	C	H	N
98		H	H	Para	183-184°	--	--	--	--	--	--

Ex.#	R^2	R^4	R^5	Position of Amide	M.P. °C	Analysis					
						Calculated %			Found %		
						C	H	N	C	H	N
99		H	H	Para	N.T.	77.09	6.49	3.60	76.75	6.67	3.55
100		CH_2CH_3	CH_2CH_3	Meta	112-114°	76.30	7.94	3.56	76.55	8.22	3.61
101		H	H	Para	169-171°	77.08	7.08	3.59	77.07	6.95	3.59
102		H	CH_3	Para	98-100°	77.39	7.24	3.47	77.31	7.24	3.45
103		H	H	Meta	151-153°	74.75	6.87	4.15	74.47	6.97	4.00

Ex.#	R^2	R^4	R^5	Position of Amide	M.P. °C	Analysis					
						Calculated %			Found %		
						C	H	N	C	H	N
104		H	H	Para	245-247°	--	--	--	--	--	--

EXAMPLE 105

N-(2-Methylphenyl)sulphonyl
4'-methoxy-3'-(1-methyl-4-phenylbutoxy)-
(+)[1,1'-biphenyl]-4-carboxamide,

To a solution of acid 4'-methoxy-3'-(1-methyl-4-phenylbutoxy)-(+)[1,1'-biphenyl]-4-carboxylic acid, (0.257 g, 0.658 mmoles) in 10 ml of anhydrous methylene chloride under hydrogen atmosphere was added dimethylamino pyridine (88.46 mg, 0.728 mmoles); o-Toluenesulfonamide (0.122 g, 0.712 mmoles) and dicyclohexylcarbodiimide (0.124 g, 0.6 mmoles) the reaction mixture allowed to stir for 50 hours. The solvent was evaporated and the resulting solid triturated with methylene chloride:ether (~1:1) which lead to precipitation of by-product DCU which was filtered. Concentration of the mother liquor followed by 3 g additional triturations with ethyl acetate/ether (~1:1) caused additional deposit of white solid which was filtered. The clear filtrate was concentrated and purified on a silica gel column using methylene chloride/methanol as eluant (95:5). Concentration of fractions containing desired products gave a total of 0.37 g of white foamy solid. Recrystallization from ethyl acetate/hexane gave 0.208 grams of white solid. M.P.: 97-100°C.

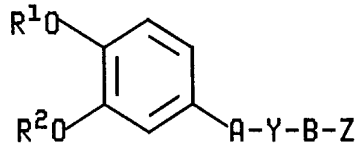
EXAMPLE 106

2-[3-[4-(4-Methoxyphenyl)butoxy]-4-methoxy
phenyl]-1H-benzimidazole-5-carboxylic Acid

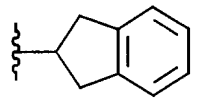
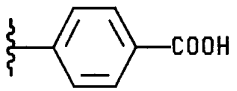
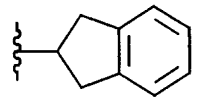
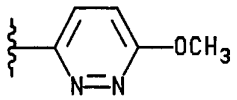
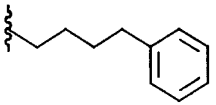
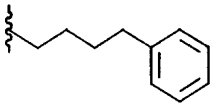
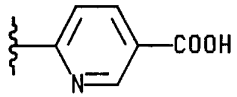
3-(4-(4-Methoxyphenyl)-butoxy)-4-methoxybenzaldehyde (2.8 g) and 3,4-diaminobenzoic acid (1.4 g) were heated to about 120°C over 1 hour. The resulting residue was chromatographed on a 5 x 10 cm pad of silica gel eluting with ether to give 1.4 g of a beige solid which was recrystallized from 20 ml of methanol. M.P. 167-169°C. MS m/e 450 ($M^+ + 1$). Elemental analysis calculated for $C_{26}H_{28}O_5N_2$: C, 69.62; H, 6.29; N, 6.24. Found: C, 69.72; H, 6.70; N, 5.75.

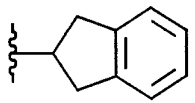
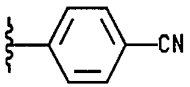
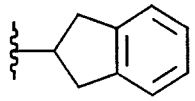
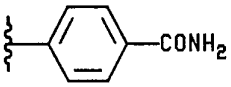
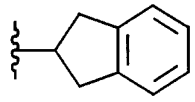
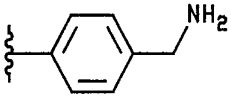
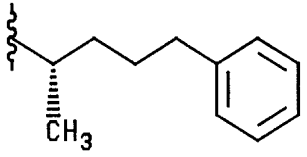
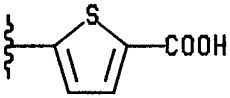
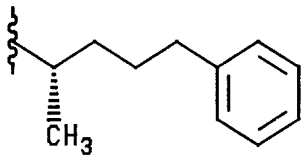
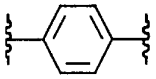
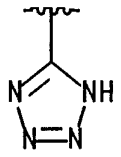
EXAMPLES 107-211

Additional examples which were prepared according to the methods described and readily apparent to those skilled in the art are shown in the following table.

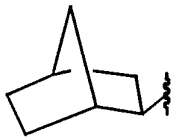
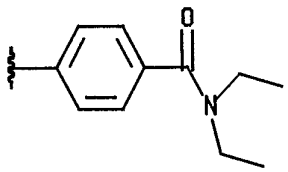
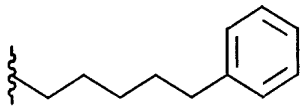
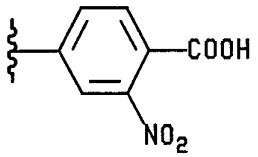
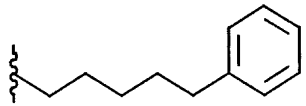
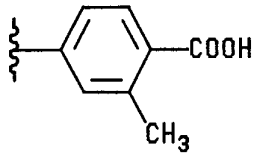
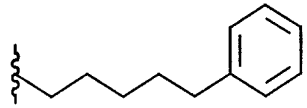
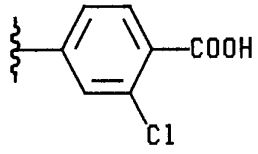


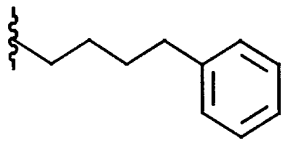
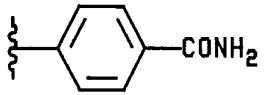
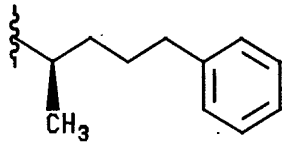
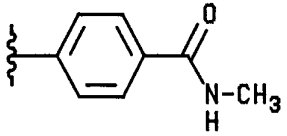
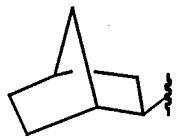
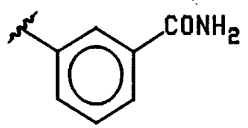
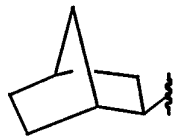
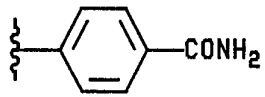
*C.B. = Covalent Bond

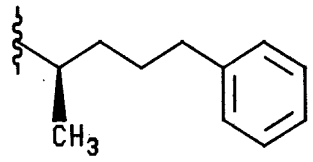
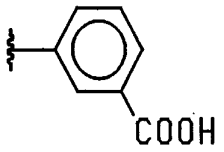
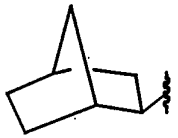
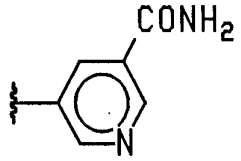
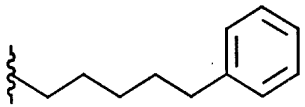
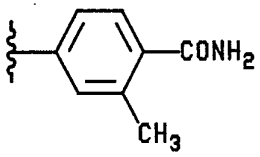
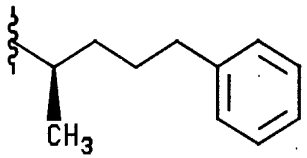
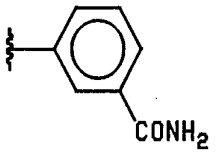
Ex. #	R^1	R^2	A	Y	B	Z-R^3	M.P.(°C)
107	CH_3		C.B.	C.B.	C.B.		244-247
108	CH_3		C.B.	C.B.	C.B.		119-122 dec.
109	CH_3		C.B.	C.B.	C.B.		118-119
110	CH_3		C.B.	C.B.	C.B.		188-189

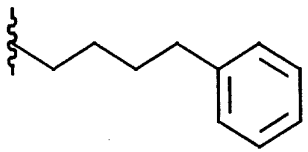
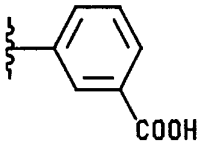
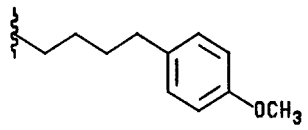
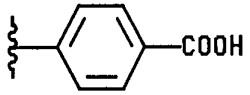
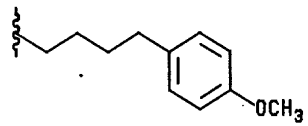
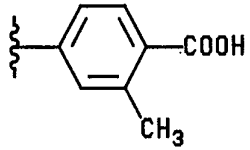
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
111	CH_3		C.B.	C.B.	C.B.		199-201
112	CH_3		C.B.	C.B.	C.B.		237-239
113	CH_3		C.B.	C.B.	C.B.		128-129
114	CH_3		C.B.	C.B.	C.B.		122-124
115	CH_3		C.B.	C.B.			139-140

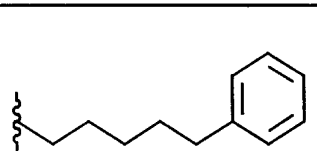
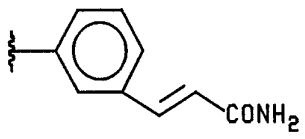
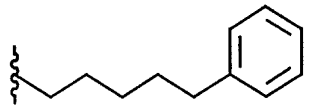
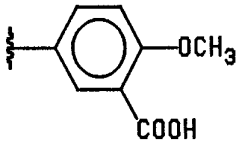
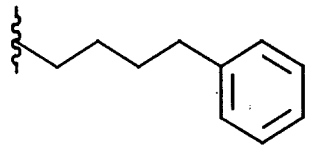
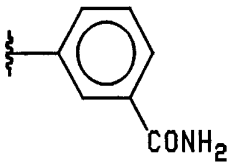
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
116	CH_3		C.B.	C.B.	C.B.		190-191
117	CH_3		C.B.	C.B.	C.B.		85-87
118	CH_3		C.B.	C.B.	C.B.		183-184
119	CH_3		C.B.	C.B.	C.B.		182-184

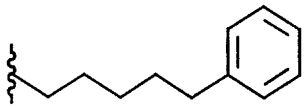
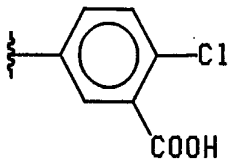
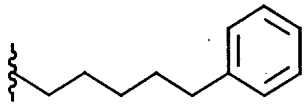
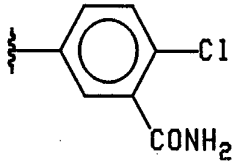
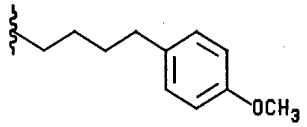
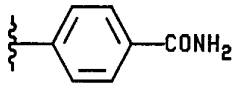
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
120	CH_3		C.B.	C.B.	C.B.		112-114
121	CH_3		C.B.	C.B.	C.B.		124-125
122	CH_3		C.B.	C.B.	C.B.		127-128
123	CH_3		C.B.	C.B.	C.B.		127-128

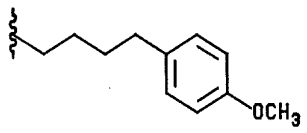
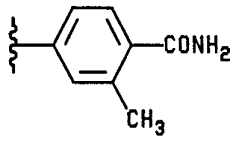
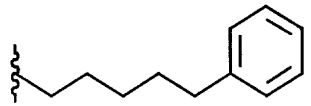
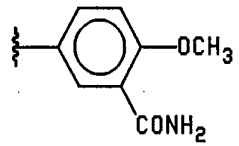
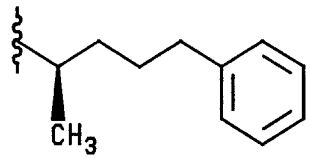
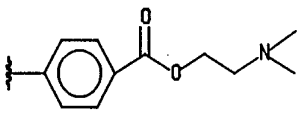
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
124	CH_3		C.B.	C.B.	C.B.		178-180
125	CH_3		C.B.	C.B.	C.B.		98-100
126	CH_3		C.B.	C.B.	C.B.		151-153
127	CH_3		C.B.	C.B.	C.B.		245-247

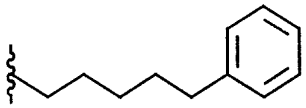
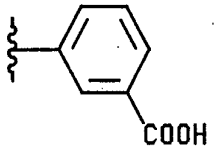
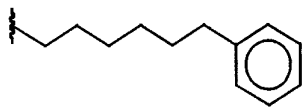
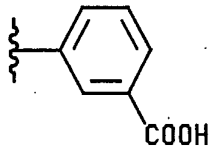
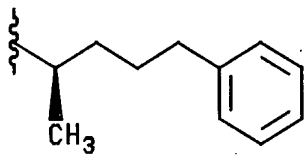
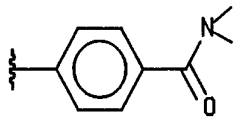
Ex. #	R^1	R^2	A	Y	B	Z-R^3	M.P.(°C)
128	CH_3		C.B.	C.B.	C.B.		47-50
129	CH_3		C.B.	C.B.	C.B.		169-171
130	CH_3		C.B.	C.B.	C.B.		153-154
131	CH_3	 (+)	C.B.	C.B.	C.B.		88-90

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
132	CH_3		C.B.	C.B.	C.B.		110-112
133	CH_3		C.B.	C.B.	C.B.		171-172
134	CH_3		C.B.	C.B.	C.B.		139-140

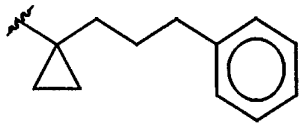
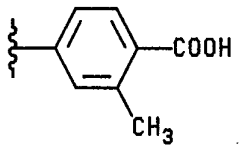
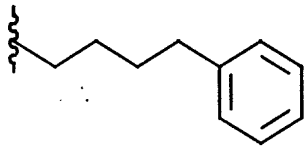
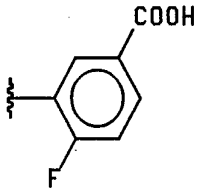
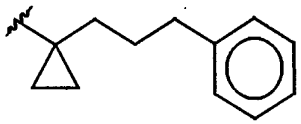
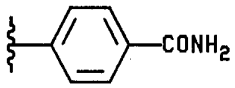
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
135	CH_3		C.B.	C.B.	C.B.		145-146
136	CH_3		C.B.	C.B.	C.B.		72-73
137	CH_3		C.B.	C.B.	C.B.		117-119

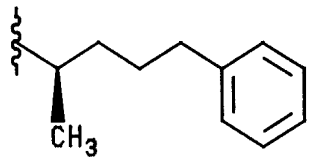
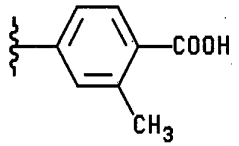
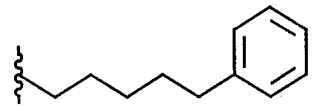
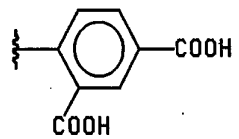
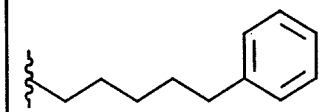
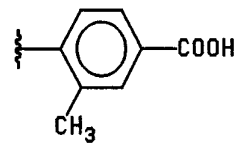
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
138	CH_3		C.B.	C.B.	C.B.		54-55
139	CH_3		C.B.	C.B.	C.B.		165-166
140	CH_3		C.B.	C.B.	C.B.		177-178

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
141	CH_3		C.B.	C.B.	C.B.		141-142
142	CH_3		C.B.	C.B.	C.B.		124-125
143	CH_3	 (+)	C.B.	C.B.	C.B.		120-123

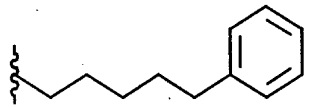
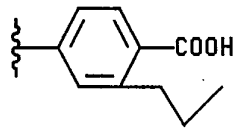
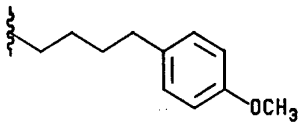
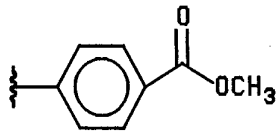
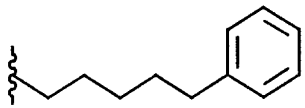
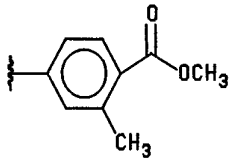
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
144	CH_3		C.B.	C.B.	C.B.		116-118
145	CH_3		C.B.	C.B.	C.B.		99-101
146	CH_3		C.B.	C.B.	C.B.		Mass Spectra $M^+ = 418$

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
147	CH_3		C.B.	C.B.	C.B.		83-84
148	CH_3		C.B.	C.B.	C.B.		118-121
149	CH_3		C.B.	C.B.	C.B.		141-142

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
150	CH_3		C.B.	C.B.	C.B.		157-158
151	CH_3		C.B.	C.B.	C.B.		116-118
152	CH_3		C.B.	C.B.	C.B.		154-155

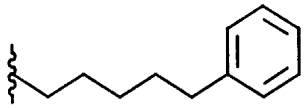
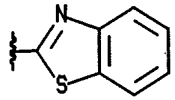
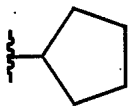
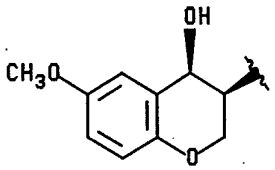
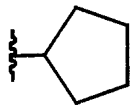
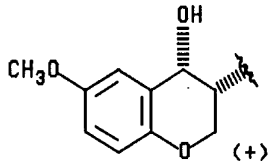
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
153	CH_3		C.B.	C.B.	C.B.		128-130
154	CH_3		C.B.	C.B.	C.B.		173-175
155	CH_3		C.B.	C.B.	C.B.		124-125

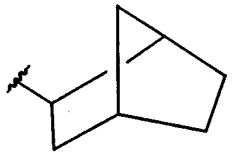
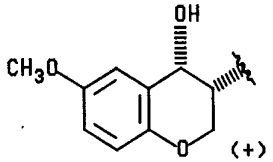
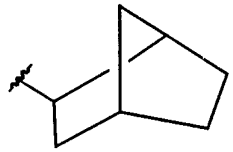
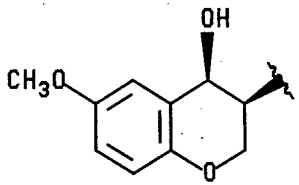
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
156	CH_3		C.B.	C.B.	C.B.		164-165
157	CH_3		C.B.	C.B.	C.B.		132-133
158	CH_3		C.B.	C.B.	C.B.		79-81

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
159	CH_3		C.B.	C.B.	C.B.		123-124
160	CH_3		C.B.	C.B.	C.B.		Mass Spectra m/e = 420
161	CH_3		C.B.	C.B.	C.B.		Mass Spectra m/e = 418

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
162	CH_3		C.B.	C.B.	C.B.		103-104
163	CH_3		C.B.	C.B.	C.B.		103-105
164	CH_3		C.B.	C.B.	C.B.		136-138

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
165	CH_3		C.B.	C.B.	C.B.		113-114
166	CH_3		C.B.	C.B.	C.B.		141-142
167	CH_3		C.B.	C.B.	C.B.		135-136

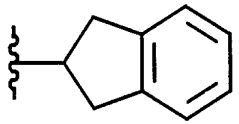
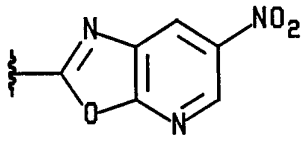
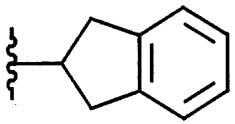
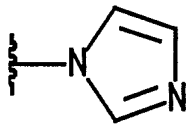
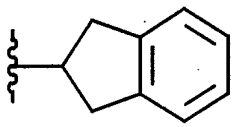
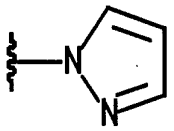
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
168	CH_3		$-CH_2-$	C.B.	C.B.		64-66
169	CH_3		$-CH_2-$	C.B.	C.B.		104-108
170	CH_3		$-CH_2-$	C.B.	C.B.		97-99

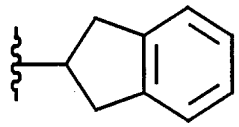
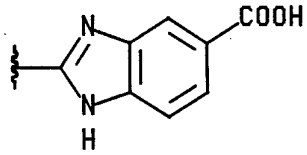
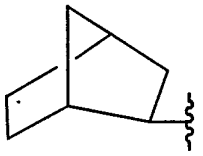
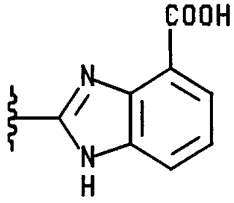
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
171	CH_3		$-CH_2-$	C.B.	C.B.	 (+)	144-146
172	CH_3	 (R)	$-CH_2-$	C.B.	C.B.	 (-)	145-147

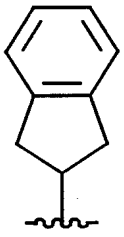
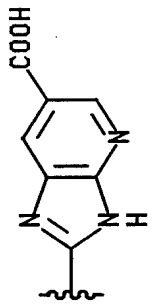
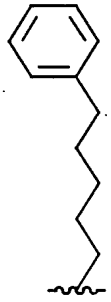
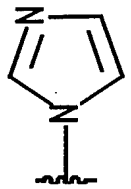
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
173	CH_3		C.B.	C.B.	$-CH_2-$	(+)	145-147
174	CH_3	(S)	C.B.	C.B.	$-CH_2-$	(-)	144-146

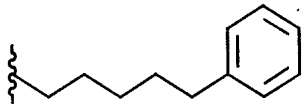
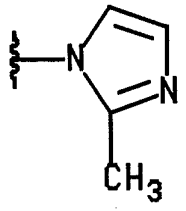
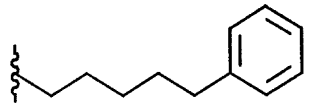
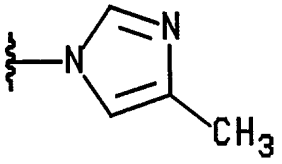
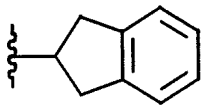
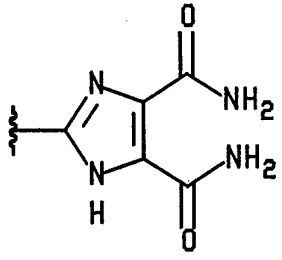
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
175	CH_3	(+)	$-CH_2-$	-O-			129-131
176	CH_3	(-)	$-CH_2-$	-O-			138-140

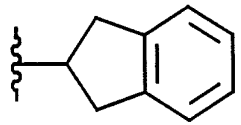
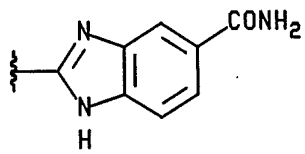
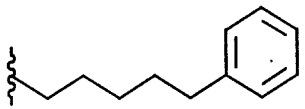
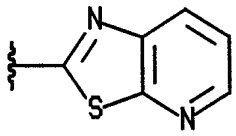
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
177	CH_3		$-CH_2-$	H -N-	C.B.		Mass Specta e/z = 383
178	CH_3		$-CH_2-$	H -N-	C.B.		92-93

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
179	CH_3		C.B.	C.B.	C.B.		228-229
180	CH_3		C.B.	C.B.	C.B.		118-119
181	CH_3		C.B.	C.B.	C.B.		110-112

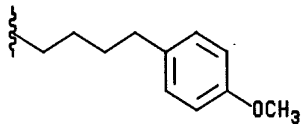
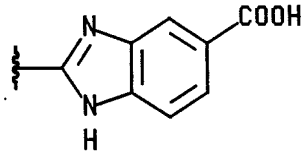
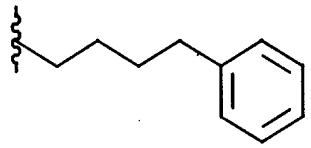
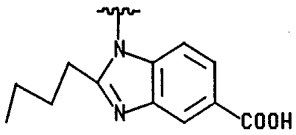
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
182	CH_3		C.B.	C.B.	C.B.		185-187
183	CH_3		C.B.	C.B.	C.B.		229-230

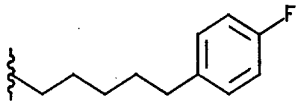
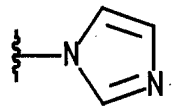
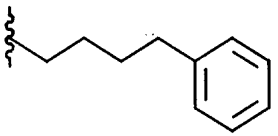
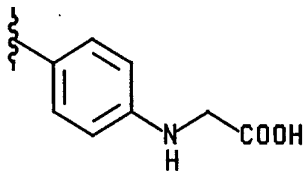
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
184	CH_3		C.B.	C.B.	C.B.		301-302 dec.
185	CH_3		C.B.	C.B.	C.B.		

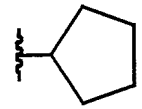
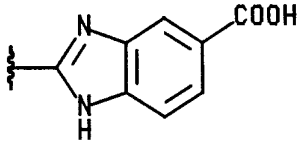
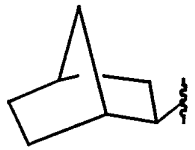
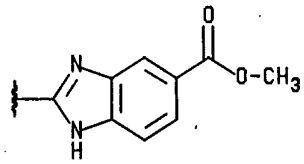
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
186	CH_3		C.B.	C.B.	C.B.		
187	CH_3		C.B.	C.B.	C.B.		71-72
188	CH_3		C.B.	C.B.	C.B.		241-242

Ex. #	R^1	R^2	A	Y	B	Z-R^3	M.P.(°C)
189	CH_3		C.B.	C.B.	C.B.		156-158
190	CH_3		C.B.	C.B.	C.B.		101-102

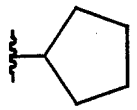
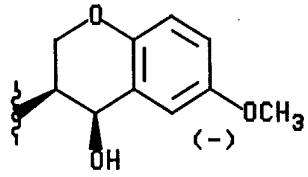
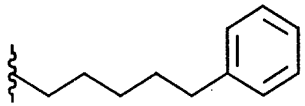
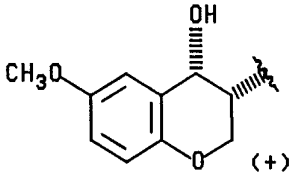
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
191	CH_3		C.B.	C.B.	C.B.		73-74
192	CH_3		C.B.	C.B.	C.B.		138-140

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
193	CH_3		C.B.	C.B.	C.B.		145-147
194	CH_3		C.B.	C.B.	C.B.		146-148

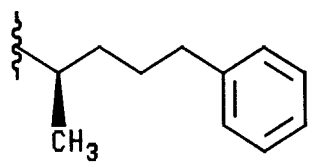
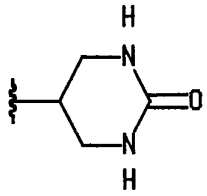
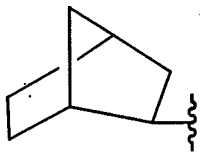
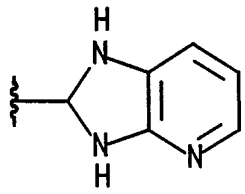
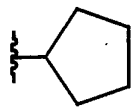
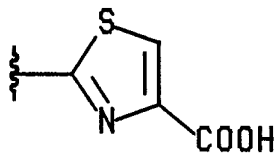
Ex. #	R^1	R^2	A	Y	B	Z-R^3	M.P.(°C)
195	CH_3		C.B.	C.B.	C.B.		Mass Spectra e/z = 355
196	CH_3		C.B.	C.B.	C.B.		High Resolution Mass Spectra Calc'd: 405.19401 Found: 405.19316

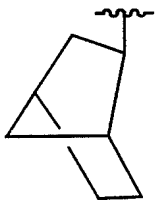
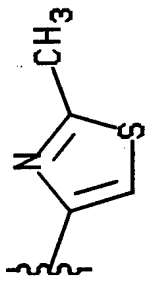
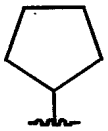
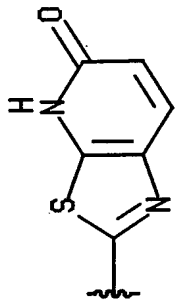
Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
197	CH_3		C.B.	C.B.	C.B.		210
198	CH_3		C.B.	C.B.	C.B.		260-262

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
199	CH_3		C.B.	C.B.	C.B.		221-223
200	CH_3		C.B.	C.B.	C.B.		68-71

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
201	CH_3		C.B.	C.B.	$-CH_2-$		105-107
202	CH_3		C.B.	C.B.	$-CH_2-$		115-119

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
203	CH_3		C.B.	C.B.	$-CH_2-$		115-119
204	CH_3		C.B.	C.B.	$-CH_2-$		96-98

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
205	CH_3		C.B.	C.B.	C.B.		131-133
206	CH_3		C.B.	C.B.	C.B.		153-154
207	CH_3		C.B.	C.B.	C.B.		123-125

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
208	CH_3		C.B.	C.B.	C.B.		81-82
209	CH_3		C.B.	C.B.	C.B.		244-247

Ex. #	R^1	R^2	A	Y	B	$Z\text{-}R^3$	M.P.(°C)
210	CH_3		C.B.	C.B.	C.B.		226-228
211	CH_3		C.B.	C.B.	C.B.		261-262

EXAMPLE 212

4-(4-Methoxy-3-(5-phenylpentyloxy)phenyl-
2-methylbenzohydroxamic acid

A solution of 2-methyl-4-[4-methoxy-3-(5-phenylpentyloxy)phenyl]benzoic acid (0.13 g, 0.32 mmoles) in oxalyl chloride (5 ml) was heated to reflux under nitrogen for about 10 minutes. The solution was concentrated under reduced pressure and the residue dried at about 25°C (0.05 mm pressure). The residue was then dissolved in dry THF (5 ml) and added slowly to a solution of hydroxylamine hydrochloride (0.022 g, 0.32 mmoles) in pyridine at about 0°C. After stirring at about 25°C for about 16 hours the volatiles were removed under reduced pressure and the residue was slurried in 1NHCl. The mixture was then extracted with ethyl acetate and the combined organics were washed with water and brine, and dried over $MgSO_4$. Filtration followed by concentration under reduced pressure yielded a beige solid. Recrystallization from isopropyl ether (10 ml) gave 0.055 grams of the title compound as an off-white solid. M.P. 125-126°C; analysis calc'd. for $C_{26}H_2gNO_4$: C, 74.43; H, 6.97; N, 3.34. Found: C, 73.85; H, 6.78; N, 3.34.

EXAMPLE 213

2-[4-Methoxy-3-(5-phenylpentyloxy)phenyl]-
1H-benzimidazole-5-carboxylic acid

A solution of 4-methoxy-3-(5-phenylpentoxy)-benzoic acid (5.0 grams, 15.9 mmole) in thromyl chloride (20 ml) was heated to reflux for about 1 hour. The mixture was concentrated under reduced pressure and the residue was dissolved in dry THF (20 ml) and added to a stirred solution of methyl-3,4-diaminobenzoate in pyridine (20 ml) at about 0°C. After about 1 hour the mixture was concentrated under reduced pressure and 1NHCl (50 ml) was added. The resulting mixture was extracted with ethylacetate (100 ml x 3) and the combined organics were washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 7.3 grams of a red foam.

The above foam was suspended in phosphorous oxychloride (50 ml) and the mixture was heated to reflux for about 1 hour. The resulting homogeneous solution was concentrated under reduced pressure; water (100 ml) was added and the mixture was neutralized to pH 7-8 with 6N NaOH. To this was added saturated aqueous bicarb. (50 ml) and the mixture was extracted with ethyl acetate (3 x 100 ml). The combined

organics were washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 6.81 grams of a tan solid.

The above solid was dissolved in a 1:1 mixture of ethanol (45 ml) and 1 N NaOH (45 ml). After stirring at reflux for about 1 hour the solution was concentrated under reduced pressure, dissolved in water (200 ml) and extracted with ether (50 ml). The aqueous layer was acidified to pH 1 with 6 N HCl and filtered. Recrystallization of the precipatate from methanol/isopropanol gave 4.4 grams of the title compound as a tan solid. MP 204-206°C; ^{1}HNMR (250 MHz, DMSO-d_6) 1.44-1.53 (m, 2H), 1.60-1.72 (m, 2H), 1.75-1.88 (m, 2H), 2.62 (t, J=7.6 Hz, 2H), 3.87 (s, 3H), 4.10 (t, J=6.6 Hz, 2H), 7.15-7.31 (m, 6H), 7.74 (d, J=8.5 Hz, 1H), 7.87-7.97 (M, 3H), 8.21 (s, 1H). Anal. calc'd for $C_{26}H_{26}N_2O_4 \bullet HCl$: C, 66.88; H, 5.83; N, 6.00. Found: C, 67.20; H, 5.75; N, 6.10.

EXAMPLE 214

4-[3-[4-(3,4-Dimethylphenyl)-4-hydroxy]butyloxy-4-methoxy]phenyl-3-methylbenzoic acid

A solution of 70 mg (0.156 mmol) of the compound of Preparation 51 in 2 ml of methanol was treated with 19 mg (0.33 mmol) of KOH, and the mixture was stirred for about 3 h at room temperature. An additional 19 mg of KOH was added, and stirring was continued for about 16 h. The mixture was heated to about 50°C for about 0.5 h, and the solvent was removed by evaporation. The residue was diluted with water, acidified with IN HCl, and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated to five 51 mg of a foam. Purification by flash chromatography using an EtOAc-hexane (1:1) eluant gave 42 mg (62%) of the title compound as a foam (R_f 0.2 EtOAc-hexane, 1:1). ^{1}H-NMR: δ1.82-1.97 (4H, m), 1.99 (3H, s), 2.00 (3H, s), 2.29 (3H, s), 3.96 (3H, s), 3.96-4.07 (2H, m) 4.6204.68 (1H, m), 6.74-7.27 (m, 7H), 7.86 (1H, d, J=8), 7.92 (1H, s) FAB MS (m/3): 434(M+), 417,258.

EXAMPLE 215

4-[3-[(4-Aminophenyl)butyloxy]-4-methoxy]phenyl-3-methylbenzoic acid

A solution of 190 mg (0.452 mmol) of the compound of Preparation 53 in a mixture of 7 ml of MeOH and 3 ml of water was treated with 20.0 mg (0.452 mmol) of NaOH, and the mixture was stirred for about 16 h at room temperature. An additional 20 mg of NaOH was added, and stirring was continued for about 24 h. The mixture was partially evaporated to remove MeOH, and the residue was carefully neutralized with 6M HCl. The oily precipitate was extracted with EtOAc (3 x 50 ml), and the combined extracts were combined, dried (Na_2SO_4), and evaporated to an oil.

Crystallization from hexane afforded 60 mg (325) of the title compound, mp 150-152°C. ^{1}H-NMR ($CDCl_3$): δ 1.76-1.99 (4H, m), 2.33 (3H, s), 3.22 (2H, t, J=7), 3.89 (3H, s), 4.06 (2H, t, J=5), 6.62-7.32 (9H, m), 8.90 (1H, d, J=8), 7.99 (1H, s). Anal. Calcd. for $C_{25}H_{27}O_4N \cdot \frac{1}{2}H_2O$: C, 72.44; H, 6.81; N, 3.38; Found C, 72.77; H, 6.56 N, 3.39.

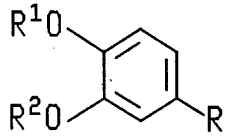
PREPARATION 1

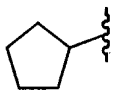
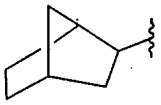
3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde

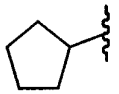
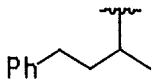
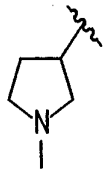
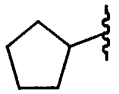
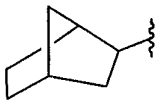
Diisopropylazodicarboxylate (7.8 ml, 39.5 mmol, 1.2 eq) was added neat to a 25° solution of (5.00 g, 32.9 mmol, 1.0 eq) 3-hydroxy-4-methoxybenzaldehyde (9.48 g, 36.1 mmol, 1.1 eq) triphenylphosphine, and (3.69 g, 32.9 mmol, 1.0 eq) (±)-endo-norborneol in 100 ml of anhydrous tetrahydrofuran. After refluxing for 6 hours, the reaction mixture was poured into 1 liter of H_2O and extracted twice with ethyl acetate. The ethyl acetate layers were combined and washed twice with H_2O, once with 1N NaOH, once with H_2O and once with brine and then the solution was dried over anhydrous sodium sulfate. Filtration, concentration, and drying afforded 26.1 g of crude product, which was chromatographed on a silica gel column, eluting with 20% ethyl acetate-hexane to afford 5.68 g, 70% yield, of a yellow oil. IR(cm^{-1}): 1680, 1580. NMR ($CDCl_3$): δ 9.82 (s, 1H), δ 4.27 (d, 1H). High resolution mass spectra (HRMS): 246.1300.

PREPARATIONS 2-8

Reaction of the appropriate vanillin with the requisite alcohol of the formula R^2-OH, analogous to the procedure of Preparation 1, afforded the following compounds:



Prep.#	R^1	R	R^2	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
							Calculated (%)		Found (%)	
							C	H	C	H
2	CH_3	3-CHO		oil	220.3	220	--	--	--	--
3	CH_3	3-OCH_3	 sm = endo prod = exo	oil	260.3	260	73.82	7.74	73.19	8.03

Prep.#	R^1	R	R^2	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
							Calculated (%)		Found (%)	
							C	H	C	H
4	CH_3	3-NO_2		63.5°	237.3	--	60.75	6.37	60.58	6.05
5	CH_3	4-CHO	 (±)	oil	284.4	284	--	--	--	--
6	CH_3	4-CHO	 (±)	oil	235.3	235	--	--	--	--
7	C_2H_5	3-CHO		oil	234.3	234	71.76	7.74	71.74	8.00
8	C_2H_5	3-CHO	 sm = endo prod = exo	oil	260.2	260	--	--	--	--

PREPARATION 9

Bis(2-methoxy-5-bromophenyl)carbonate

Dissolved (8.26 ml, 160 mmol, 2.2 eq) bromine in 10 ml of $CHCl_3$ and then added it dropwise over 10 minutes to (20.0 g, 72.9 mmol, 1.0 eq) of bis(2-methoxyphenyl)carbonate in 60 ml of $CHCl_3$ at room temperature. Stirred for 60 minutes at room temperature, then filtered the reaction mixture, washing the precipitate three times with $CHCl_3$ and once with hexane. The precipitate was recrystallized from $CHCl_3$ to yield 20.7 g, 66% yield, of bis(2-methoxy-5-bromophenyl)carbonate as white prisms.

PREPARATION 10

5-Bromoguaiacol

A suspension of (20.7 g, 47.9 mmol, 1.0 eq) bis(2-methoxy-5-bromophenyl)-carbonate in 250 ml methanol and 60 ml (120 mmol, 2.5 eq) of 2N NaOH was refluxed for 2 hours. The reaction mixture was cooled to room temperature, concentrated to a volume of ca 100 ml, and poured into 1 L of H_2O. The pH was adjusted to 2 using 1N HCl. The acidic mixture was transferred to a separatory funnel, and extracted three times with ether. The ether extracts were combined and washed once with H_2O, once with brine, and then dried over anhydrous sodium sulfate. Filtration, concentration and drying afforded 19.0 g of a white solid, which was recrystallized from petroleum ether to yield 17.63 g, 91% yield, of white prisms.

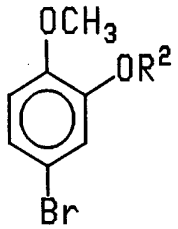
PREPARATION 11

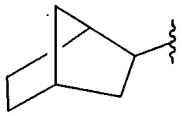
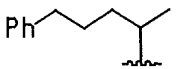
2-(5-Bromo-2-methoxyphenoxy)bicyclo[2.2.1]heptane

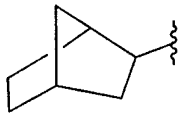
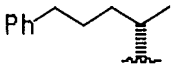
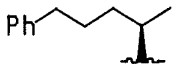
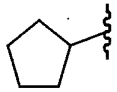
Neat diethylazodicarboxylate (1.4 ml, 8.87 mmol, 1.2 eq) was added to a 25°C solution of (1.50 g, 7.39 mmol, 1.0 eq) 5-bromoguaiacol, (2.13 g, 8.13 mmol, 1.1 eq) triphenylphosphine and (0.829 g, 7.39 mmol, 1.0 eq) of S(-)endo-norborneol in 25 ml of anhydrous tetrahydrofuran. After stirring 18 hours at room temperature under N_2, the reaction mixture was diluted with 350 ml of ether, washed twice with 1N NaOH, once with H_2O, once with brine, and then dried over anhydrous Na_2SO_4. Filtration, concentration and drying afforded a yellow oil which was triturated with ca 250 ml of 1:1 ether-hexane to remove triphenylphosphine oxide. The filtrate was concentrated in vacuo, and chromatographed on a silica gel column, eluting with 10% ethyl acetate-hexane, to afford 1.75 g, 80% yield, of a clear, colorless oil. Elemental Analysis: Calc'd for $C_{14}H_{17}O_2Br$: Calc'd: C, 56.57; H, 5.77%. Found: C, 56.68; H, 5.73%.

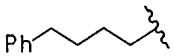
PREPARATIONS 12-18

Reaction of 5-bromoguaiacol with the requisite alcohol of the formula R^2-OH, analogous to the procedure of Preparation 11, afforded the following compounds:



Prep.#	R^2	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
12	 endo = sm exo = prod	oil	297.3	298	--	--	--	--
13		oil	349.3	350	--	--	--	--

Prep.#	R^2	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
14	 R(+) = sm S(+) = prod	oil	297.2	298	56.57	5.77	56.74	5.72
15	 R(-) = sm S(+) = prod	oil	349.29	349.2	61.89	6.09	61.18	6.10
16	 S(+) = sm R(+) = prod	oil	349.29	349.2	61.89	6.09	59.77	5.66
17		oil	271.17	271.1	53.16	5.58	53.41	5.62

Prep.#	R^2	M.P. °C	M.W.	Mass Spec (M+)	Analysis			
					Calculated (%)		Found (%)	
					C	H	C	H
18		oil	335.26	--	--	--	--	--

sm = starting material
prod = product

PREPARATION 19

4-(Difluoromethoxy)-3-hydroxybenzaldehyde

Dissolved (5.00 g, 36.2 mmol, 1.0 eq) of 3,4-dihydroxybenzaldehyde in 60 ml of 1,4-dioxane, then added 24 ml of H_2O and 36.2 ml (72.4 mmol, 2.0 eq) of 2N NaOH to the above solution at room temperature. After heating to 70°C external, chlorodifluoromethane was bubbled into the reaction mixture for 50 minutes, maintaining a temperature of 60-70°C. The reaction mixture was cooled to room temperature, concentrated in vacuo, diluted with 1 L H_2O and the pH adjusted to 5 using 1N HCl. The aqueous layer was then transferred to a separatory funnel, extracted four times with 300 ml each of ethyl acetate. The ethyl acetate layers were combined and washed once with brine and dried over anhydrous Na_2SO_4. The crude product was chromatographed over silica gel eluting with 25% ethyl acetate-hexane. Yield was 1.30 g, 19%, as a white solid. Elemental Analysis: Calc'd for $C_8H_6O_3F_2$: Calc'd: C, 51.08; H, 3.22. Found: C, 51.10; H, 3.14. NMR (300 MHz, $CDCl_3$): δ 6.65 (1H, t), δ 9.91 (1H, s). M.P.: 82-83°C.

PREPARATION 20

3-(Difluoromethoxy)-4-hydroxybenzaldehyde

The title compound is prepared according to the reaction procedure of Preparation 19. The title product was isolated from the reaction mixture by column chromatography. M.P.: 64-66°C. NMR (300 MHz, $CDCl_3$): δ 6.61 (1H, t), δ 9.83 (1H, s).

PREPARATION 21

3-Bicyclo[2.2.1]hept-2-yloxy-4-difluoromethoxybenzaldehyde

Into a stirred solution of (3.28 g, 14.1 mmol, 1.0 eq) of (±)-3-exo-norbornyloxy-4-hydroxybenzaldehyde in 200 ml of 2N NaOH and 100 ml of dioxane at 70°C was bubbled in HCF_2Cl gas. The reaction mixture was poured into 400 ml of H_2O, acidified, and extracted with ether twice. The ether extracts were combined, washed twice with saturated $NaHCO_3$ solution, once with H_2O, once with brine, and dried over $MgSO_4$, then concentrated to yield 4 g of crude product. Flash chromatography on silica gel eluting with 15% ethyl acetate-hexane yielded 1.3 g, 33%, of an oil. Mass Spectra (M+): 282. NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), δ 6.64 (t, 1H).

PREPARATION 22

3-(Bicyclo[2.2.1]hept-2-yloxy)-
4-hydroxybenzaldehyde

A mixture of (500 mg, 2.03 mmol, 1.0 eq) (±)-3-exo-norborynloxy-4-methoxy-benzaldehyde and (201 mg, 2.87 mmol, 1.4 eq) sodium thiomethoxide in 10 ml of anhydrous DMF was heated at 50-60°C for 20 hours. The reaction mixture was poured into 150 ml 0.5 N HCl and extracted twice with ether. The ether extracts were combined, washed twice with saturated $NaHCO_3$, once with H_2O, once with brine, dried over $MgSO_4$, and then concentrated to give 0.5 g of an oil. Flash chromatography on silica gel, eluting with 15% ethyl acetate/hexane, yielded 320 mg, 72%, of an oil. Mass Spectra (M+): 232. NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1H).

PREPARATION 23

2-Bicyclo[2.2.1]hept-2-yloxy)-
4-[(methylthio)methyl]phenol

A solution of (9.00 g, 122 mol, 5.0 eq) sodium thiomethoxide, (6.00 g, 24.4 mmol, 1.0 eq) (±)-3-exo-norbornyloxy-4-methoxybenzaldehyde in 120 ml of anhydrous dimethylformamide was heated to reflux under N_2 for 45 minutes. The reaction mixture was cooled, poured into 500 ml of 0.5 N HCl, extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed four times with H_2O, once with brine, dried over Na_2SO_4, and then concentrated to yield 6.85 g of a brown oil. Silica gel chromatography eluting with 10% ethyl acetate-hexane afforded 1.47 g, 26%, of a pale yellow oil. Elemental Analysis: Calcd. for $C_{15}H_{20}O_2S$: Calc'd: C, 68.14; H, 7.62; S, 12.13. Found: C, 68.10; H, 7.28; S, 12.38. M.P. = 75-77°C.

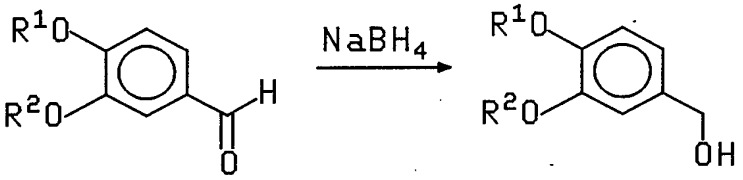
PREPARATION 24

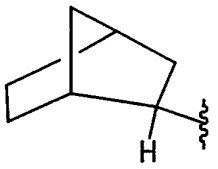
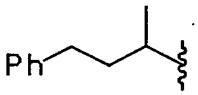
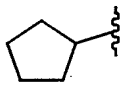
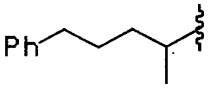
3-(Bicyclo[2.2.1]hept-2-yloxy-4-
methoxy-α-methylbenzenemethanol

Added (108 mg, 2.85 mmol, 1.1 eq) sodium borohydride to a stirred solution of (675 mg, 2.59 mmol, 1.0 eq) (±)-3-methoxy-4-exo-norbornyloxy-acetophenone in 15 ml MeOH and 15 ml tetrahydrofuran. After 2 hours at room temperature, the reaction mixture was concentrated, poured into 200 ml of ethyl acetate, washed once with H_2O, once with brine, dried over Na_2SO_4, and then concentrated to yield 0.72 g of a clear oil. Silica gel chromatography eluting with 10% ethyl acetate/CH_2Cl_2 afforded 672 mg, 99%, of a clear oil. Mass spectra (M+): 262.

PREPARATIONS 25-28

Reaction of the following aldehydes, analogous to the procedure of Preparation 24 afforded the corresponding alcohols:



Prep.#	R^2	R^1	M.W.	Mass Spec. (M+)
25		HF_2C	284.3	284
26		H_3C	286.4	286
27	H_3C		222.2	--
28		H_3C	300.4	300

PREPARATION 29

3-Cyclopentyl-4-methoxybenzoic acid

To a stirred suspension of (5.0 g, 27 mmol, 1.0 eq) methyl vanillate, (2.5 ml, 27 mmol, 1.0 eq) cyclopentanol, and (7.4 g, 28 mmol, 1.05 eq) triphenylphosphine in 40 ml of anhydrous tetrahydrofuran was added (4.7 ml, 29.7 mmol, 1.1 eq) of diethylazodicarboxylate. The reaction mixture was stirred 18 hours at room temperature, concentrated in vacuo, and flash chromatographed on a silica gel column, eluting with 20%

ethyl acetate/hexane, to yield 7.0 g, >100%, of an oil, methyl-3-methoxy-4-cyclopentyl-oxybenzoate.

A mixture of (7.0 g, 27 mmol, 1.0 eq) methyl-3-methoxy-4-cyclopentyloxy benzoate, 8 ml (42 mmol, 1.5 eq) 5N NaOH and 40 ml MeOH was refluxed for 3 hours. The mixture was concentrated to ca 20 ml, poured into 400 ml H_2O (pH 10) and washed twice with ether. The aqueous layer was acidified to pH 1 and extracted twice with ether. The ether extracts were combined, washed once with H_2 O, once with brine, dried over $MgSO_4$ and then concentrated to yield 6 g of a white solid. Recrystallization from ether-hexane yielded 5.60 g, 88%, of white crystals. Elemental Analysis: Calcd. for $C_{13}H_{16}O_4$: Calc'd: C, 66.09; H, 6.83. Found: C, 66.20; H, 6.64.

PREPARATION 30

3-Cyclopentyloxy-4-methoxybenzylbromide

To a stirred solution of (4.4 g, 20 mmol, 1.0 eq) 3-cyclopentyloxy-4-methoxy-benzyl alcohol in 100 ml anhydrous tetrahydrofuran at 0°C was added portionwise (9.2 g, 22 mmol, 1.1 eq) dibromotriphenylphosphorane over 10 minutes. The reaction was stirred at 0°C for 1 hour, then allowed to warm to room temperature over 2 hours. The mixture was poured into 400 ml H_2O and extracted twice with 400 ml ether. The ether extracts were combined, washed once with saturated $NaHCO_3$, once with H_2O, once with brine, dried over $MgSO_4$, and then concentrated to give 10 g of a solid. Trituration with 10% ether-hexane followed by concentration of the filtrate gave ca. 2 g of an oil. Flash chromatography on silica gel eluting with 15% ethyl acetate-hexane yielded 2.17 g, 38%, of an oil.

PREPARATION 31

Phosphonium, [3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxy]methyl]triphenyl-, bromide

A mixture of (2.1 g, 7.36 mmol, 1.0 eq) 3-cyclopentyloxy-4-methoxybenzyl-bromide and (1.93 g, 7.36 mmol, 1.0 eq) triphenylphosphine in 50 ml of anhydrous toluene was heated to reflux for 18 hours. The resulting suspension was diluted with 50 ml hexane, cooled to 0°C, and filtered. The filtrant was washed with hexane and dried to yield 3.02 g, 73%, of a solid. M.P. = 228-230°C.

PREPARATION 32

1-(5-Bromo-2-methoxyphenoxy)-1-(3-phenylpropyl)cyclopropane

(a) Preparation of 2-(5-bromo-2-methoxyphenoxy)-5-phenyl-1-pentene

Tebbe reagent (prepared from titanocene dichloride and trimethyl aluminum) (30 ml of a 0.55M solution in toluene) was added dropwise to a solution of (5-bromo-2-methoxyphenyl)-1-phenylbutyrate, pyridine (0.25 ml), anhydrous tetrahydrofuran (10 ml), and anhydrous toluene (30 ml) at about 0°C. The reaction mixture was warmed to room temperature for about 2 hours, re-cooled to about 0°C and quenched with 3N sodium hydroxide (6 ml). After gas evolution had ceased, ether was added and the mixture was dried over sodium sulfate, filtered and concentrated in vacuo. Chromatography through a short column of basic alumina eluted with 25% petroleum ether/ether afforded 4.4 g of a yellow oil. Mass spectra calculated for $C_{18}H_{19}BrO_2$: 347.2. Found: 347.

(b) Preparation of the title compound

The above oil (4.4 g) was dissolved in anhydrous ether (8 ml) and treated with methylene iodide (1.2 ml) followed by zinc-copper couple (0.9 g) and iodine (5 mg). After heating at reflux for about 17 hours the mixture was filtered and the solid washed with ether. The combined organics were washed with saturated aqueous ammonium chloride, saturated aqueous bicarbonate, brine, dried over sodium sulfate, filtered and concentrated in vacuo. Chromatography on silica gel column eluting with ethyl acetate-hexane (0-10%) afforded 3.2 g of a colorless oil. Mass spectra calculated for $C_{19}H_{21}BrO_2$: 361.3. Found: 362.

PREPARATION 33

3'-Bicyclo[2.2.1]hept-2-yloxy-4'-methoxy)-1,1'-biphenyl-4-amino

A mixture of (1.7 g, 5.01 mmol, 1.0 eq) of 2-[(4-methoxy-4'-nitro-[1,1'-biphenyl]-3-yl)oxy]bicyclo[2.2.1]heptane and 1.5 g of 10% Pd/C in 100 ml ethyl acetate was shaken on a Parr hydrogenation apparatus under 40 psi H_2 at room temperature for 10 minutes. The reaction mixture was filtered through celite, concentrated in vacuo, and the residue chromatographed on silica gel eluting with CH_3OH-CH_2Cl_2 (1% → 2½%) to afford 1.45 g, 95%, of a white waxy solid. M.P.: 46-50°C.

PREPARATION 34

3-[3-Bicyclo[2.2.1]hept-2-lyoxy)-4-(difluoromethoxy)phenyl]pentanediamide

A mixture of (3.40 g, 12.0 mmol, 1.0 eq) 3-(bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxybenzaldehyde, (334 μl, 3.37 mmol, 0.28 eq) piperidine and (3.06 g, 36.0 mmol, 3.0 eq) cyanoacetic acid in 50 ml of anhydrous pyridine was heated to reflux for 17 hours. The reaction mixture was cooled to room temperature, diluted with H_2O and extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed twice with 1N HCl, once with saturated $NaHCO_3$, once with H_2O, once with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on a silica gel column eluting with 1:3 ethyl acetate:hexane to yield 2.13 g, 51%, of a yellow oil. Elemental Analysis: Calc'd for $C_{19}H_{20}N_2O_2F_2$: Calc'd: C, 65.87; H, 5.82; N, 8.09. Found: C, 65.53; H, 5.63; N, 8.25.

H_2O_2 (250 ml of 30%, 29.2 mmol, 5.0 eq) was added dropwise to a 0°C mixture of (2.02 g, 5.83 mmol, 1.0 eq) 2-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxyphenyl]propane-1,3-dinitrile and 1.67 ml of 10% aqueous Na_2CO_3 in 30 ml of acetone and 15 ml of H_2O. After stirring 1 hour at 0°C, the reaction mixture was allowed to warm to room temperature and was left stirring for 72 hours. The reaction mixture was poured into 550 ml of ethyl acetate and 400 ml of H_2O and stirred for 1 hour. The 2 layers were separated, and the aqueous layer was extracted four times with ethyl acetate. The ethyl acetate extracts were combined, washed once with H_2O, once with brine, dried over Na_2SO_4 and concentrated to yield 2.0 g of a white solid. Silica gel chromatography eluting with 10% CH_3OH-CH_2Cl_2 afforded 1.29 g, 58%, of a white powder. M.P.: 168-169°C. Elemental Analysis: Calc'd for $C_{19}H_{24}N_2O_4F_2$: Calc'd: C,59.67; H, 6.33; N, 7.33. Found: C,59.60; H, 5.99; N, 7.11.

PREPARATION 35

Methyl 2-butyl-1-(4-hydroxyphenyl)-1H-benzimidazole-5-carboxylate

A mixture of (1.5 g, 6.98 mmol, 1.0 eq) methyl-3-nitro-4-chlorobenzoate and (760 mg, 6.98 mmol, 1.0 eq) 4-aminophenol in 30 ml dry dimethylsulfoxide was heated to reflux for 18 hours. The mixture was poured into 300 ml of H_2O, acidified to pH 5 and extracted once with ether. The resulting sludge was filtered through celite, and the filtrate layers separated. The aqueous layer was extracted with ether, and the ether extracts were combined, washed twice with H_2O, once with brine, dried over $MgSO_4$,

and concentrated to give 3.0 g of an oil. Silica gel chromatography eluting with 30% ethyl acetate-hexane gave 850 mg, 42%, of a dark red gum.

A mixture of (850 mg, 2.95 mmol, 1.0 eq) of methyl 4-[(4-hydroxyphenyl)amino]-3-nitrobenzoate and 850 mg of 10% Pd/C in 40 ml ethyl acetate was placed on a Parr hydrogenation apparatus and shaken for 3 hours under 40 psi H_2. The mixture was filtered through celite, concentrated, and chromatographed on a silica gel column eluting with 40% ethyl acetate/hexane to yield 470 mg, 56%, of an off-white solid.

A mixture of (436 mg, 1.69 mmol, 1.0 eq) methyl 4-[4-hydroxyphenyl)amino]-2-aminobenzoate and 3 ml of valeric anhydride was heated to reflux for 3 hours. The reaction mixture was cooled to room temperature and flash chromatographed on a silica gel column eluting with 10% ethyl acetate/CH_2Cl_2 to give an oil, which was taken up in 15 ml MeOH and treated with 5 ml 1N NaOH for 1 hour. The mixture was poured into 300 ml of H_2O, acidified to pH 5 and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 0.6 g of an oil. Flash chromatography on silica gel eluting with 2½% CH_3OH/CH_2Cl_2 gave 345 mg, 63%, of white foam. Mass Spectra: 324.2.

PREPARATION 36

4-3H-Imidazo[4,5-b]-2-butylpyridinephenol

A mixture of (1.0 g, 4.33 mmol, 1.0 eq) 4-[(2-nitro-4-pyridinyl)amino]phenol and 500 mg of 10% Pd/C in 100 ml of tetrahydrofuran and 100 ml of methanol was placed on a Parr hydrogenation apparatus and shaken under 50 psi H_2 for 1 hour. The reaction mixture was filtered through celite and the filtrate concentrated in vacuo to give 1.01 g, >100%, of a tan solid.

A mixture of 900 mg (4.47 mmol, 1.0 eq) of the above diamine in 10 ml of valeric anhydride was heated to reflux for 3 hours. The reaction mixture was poured into 150 ml of 0.5N HCl, stirred 5 minutes, washed once with ether and the ether wash extracted with 0.5N HCl. The acidic extracts were combined, basified to pH 10 and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed once with 0.5N NaOH, once with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 1 g of an oil. Silica gel chromatography eluting with 5% CH_3OH/CH_2Cl_2 gave 900 mg, 57%, of an oil.

A mixture of (908 mg, 2.47 mmol, 1.0 eq) butyl 4-(2-butyl-1H-imidazo[4,5-c]pyridin-1-yl)benzoate and 6 ml (6 mmol, 5.0 eq) of 1N NaOH in 25 ml methanol was

stirred at room temperature for 2 hours. The reaction mixture was concentrated to ca. 10 ml, poured into 200 ml of H_2O, and extracted twice with ether. The aqueous layer was neutralized and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed once with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 1 g of solid. Silica gel chromatography eluting with 10% CH_3OH/CH_2Cl_2 yielded 590 mg, 89%, of white solid. M.P.: 161-163°C.

PREPARATION 37

4-(2-Methyl-3H-imidazo[4,5-b]pyridin-3-yl)phenol

A mixture of (3.5 g, 22 mmol, 1.0 eq) 2-chloro-3-nitro-pyridine, (3.65 g, 22 mmol, 1.0 eq) KI, (1.85 g, 22 mmol, 1.0 eq) $NaHCO_3$, and (2.40 g, 22 mmol, 1.0 eq) 4-amino-phenol in 25 ml of dry dimethylformamide was heated to reflux for 18 hours. The mixture was poured into 400 ml of H_2O, neutralized to pH 7 and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed twice with 5% $Na_2S_2O_3$, once with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 4.8 g of a black solid. Flash chromatography on silica gel eluting with 50% ethyl acetate/CH_2Cl_2, followed by crystallization from isopropyl ether/CH_2Cl_2 gave 3.7 g, 73%, of an orange-red solid.

A mixture of (3.6 g, 15.6 mmol, 1.0 eq) the nitropyridine and 0.9 g of 10% Pd/C in 50 ml of tetrahydrofuran and 50 ml of methanol was placed on a Parr hydrogenation apparatus and shaken under 50 psi H_2 for 1 hour. The mixture was filtered through celite, concentrated in vacuo (4 g purple solid), and flash chromatographed on a silica gel column eluting with 10% CH_3OH/CH_2Cl_2 to give 3.5 g of solid. Trituration from ethyl acetate gave 3.0 g, 96%, of a pink solid.

A mixture of (1.0 g, 4.97 mmol, 1.0 eq) 4-[(3-amino-2-pyridinyl)amino]phenol in 25 ml of valeric anhydride was heated to reflux for 8 hours. The reaction mixture was cooled, poured into 150 ml of 0.5N HCl, stirred 10 minutes, and extracted twice with ether. The ether extracts were combined, washed three times with saturated $NaHCO_3$, once with H_2O, once with brine, dried over $MgSO_4$, and concentrated to give an oil. The oil was taken up in 100 ml CH_3OH and treated with 60 ml of 2N NaOH and allowed to stir at room temperature for 1 hour. The mixture was concentrated, poured into 200 ml of H_2O and washed twice with ether. The aqueous layer was neutralized, and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed

once with H_2O, dried over $MgSO_4$, and concentrated to give 0.7 g of a solid. Silica gel chromatography eluting with 10% CH_3OH/CH_2Cl_2 gave 510 mg, 38%, of a solid. M.P.: 268-269°C.

PREPARATION 38

2-Butyl-3-(4-hydroxyphenyl)benzimidazole

A mixture of (8.0 g, 51 mmol, 1.0 eq) 1-chloro-2-nitrobenzene and (5.54 g, 51 mmol, 1.0 eq) 4-aminophenol in 40 ml of dry dimethylsulfoxide was heated to reflux for 18 hours. The reaction mixture was cooled, poured into 400 ml of 0.1N HCl and 400 ml ethyl acetate, stirred, and filtered through celite. The filtrate layers were separated, and the aqueous layer was extracted with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H_2O, once with brine, dried over $MgSO_4$, and concentrated to give 8 g of a dark oil. Silica gel chromatography eluting with 20% ethyl acetate/hexane gave 1.63 g, 14%, of a red solid.

A mixture of (1.6 g, 6.89 mmol, 1.0 eq) 4-N-(2-nitrophenyl)amino phenol and 800 mg of 10% Pd/C in 100 ml ethyl acetate was placed on a Parr hydrogenation apparatus and shaken under 50 psi H_2 for 3 hours. The mixture was filtered through celite, concentrated in vacuo, and chromatographed on a silica gel column eluting with 50% ethyl acetate/hexane to give 1.3 g, 94%, of an orange-yellow solid.

A mixture of (600 mg, 3.00 mmol, 1.0 eq) 4-N-(2-aminophenyl)amino phenol and 10 ml valeric anhydride was heated to reflux for 18 hours. The mixture was taken up in 50 ml of methanol, basified with 2N NaOH to pH 10, and stirred 1 hour at room temperature. The reaction mixture was then neutralized and extracted twice with ethyl acetate. The ethyl acetate extracts were combined, washed twice with H_2O, once with brine, dried over $MgSO_4$ and concentrated to give 1 g of an oil. Silica gel chromatography eluting with 2½% CH_3OH-CH_2Cl_2 gave 124 mg, 16%, solid. M.P.: 192-194°C.

PREPARATION 39

4'-Methoxy-3'-(1-methyl-4-phenylbutoxy)-
[1,1'-biphenyl]-4-carbonitrile

To a solution of (1.4 g, 4.01 mmol, 1.0 eq) of (±)-1-methoxy-2-exo-norbornyloxy-4-bromobenzene in 40 ml dry THF at -78°C was added dropwise 1.76 ml (4.4 mmol, 1.1 eq) of 2.5M n-BuLi. After stirring 40 minutes at -78°C, (4.81 ml, 4.81 mmol, 1.2 eq) 1.0M $ZnCl_2$ in ether was added, and the mixture warmed to room temperature over 30 minutes. Pd $(PPh_3)_4$ (231 mg, 0.2 mmol, 0.05 eq) and (918 mg, 4.01 mmol, 1.0 eq) 4-iodobenzonitrile were added, and the mixture stirred 2 hours at room temperature. The

reaction mixture was concentrated in vacuo and chromatographed on silica gel eluting with ether-hexane (5-30%) to afford 1.1 g, 74%, of 4'-methoxy-3'-(1-methyl-4-phenylbutoxy)-[1,1'-biphenyl]-4-carbonitrile. NMR (250 MHz, $CDCl_3$): 7.70 (2H, m); 7.59 (2H, m); 7.17 (7H, m); 6.96 (1H, m); 4.42 (1H, m); 3.90 (3H, s); 1.35 (3H, d, J=6.1 Hz).

PREPARATION 40

Methyl 1-(3-hydroxy-4-methoxyphenyl)-
1H-benzimidazole-5-carboxylate

A mixture of (10 g, 74.5 mmoles) 5-amino-2-methoxyphenol and (13.3 g, 62 mmoles) methyl 3-nitro-4-chlorobenzoate in 50 ml of pyridine was stirred at room temperature overnight. The volatiles were removed in vacuo and the residue was dissolved in ethyl acetate and washed with dilute HCl, then dried over $MgSO_4$ and evaporated to give 12.7 g of crude product which was triturated with CH_2Cl_2 and filtered to give 3.9 g of purified methyl 4-N(4-methoxy-3-hydroxyphenyl)amino-3-nitrobenzoate.

A solution of 3.9 g of the above nitro compound in 75 ml of methanol and 50 ml of THF and 400 mg of 10% palladium on charcoal was shaken on a Parr shaker, at 40 psi H_2 for 5 hours. The catalyst was removed by filtration and the solvent evaporated in vacuo. The product methyl 4-N(4-methoxy-3-hydroxyphenyl)amino-3-aminobenzoate (3.4 g) was used without purification.

A mixture of 3.4 g of the above amine and 900 mg of ethyl formate in 25 ml of formic acid was heated at 100° overnight. The solvents were evaporated in vacuo to give 1.6 g of the title product.

PREPARATION 41

2-N[3-(Cyclopentyloxy)-4-methoxyphenyl-
carbonyl]amino-3-hydroxypyridine

A mixture of (1.2 g, 5 mmoles) of 4-methoxy-3-cyclopentyloxybenzoic acid and 25 ml of thionyl chloride was heated at reflux for 30 minutes. Excess thionyl chloride was removed in vacuo and the resulting acid chloride was used without purification.

The crude acid chloride from above was dissolved in THF and was added to a solution of 600 mg of 2-amino-3-hydroxypyridine in 5 ml of pyridine at 0°C. After stirring at 0°C for 2 hours, the reaction was allowed to stir at room temperature overnight. The volatiles were evaporated and the residue was triturated with H_2O and filtered to give 1.4 g of the desired amide. M.P. 165-166°C.

PREPARATION 42

3-Cyclopentyloxy-4-methoxybenzthioamide

4-Methoxy-3-cyclopentyloxybenzoic acid was converted to its acid chloride analogous to the procedure of Preparation 41.

The acid chloride (500 mg) was dissolved in 10 ml of THF and added dropwise to a solution of aqueous ammonium hydroxide at 0°C. After 30 minutes the reaction was extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 420 mg of product. M.P.: 167-168°C.

A mixture of 400 mg of the amide and 413 mg of Lawesson's reagent in 20 ml of toluene was heated at reflux for 1 hour. The volatiles were evaporated and the residue purified on silica gel with CH_2Cl_2/methanol to give 220 mg of product. M.P.: 145-147°C.

PREPARATION 43

4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-methylthiazole

4-Methoxy-3-norbornyloxybenzoic acid was converted to the corresponding acid chloride using the procedure of Preparation 41.

To a solution of 6.9 gm of the acid chloride in 50 ml of ether was added dropwise to a solution of 2 equivalents of diazomethane in ether. The resulting diazoketone was then converted to chloromethyl ketone by addition of excess HCl(g). Evaporation of the volatiles gave 3.5 g of chloromethyl ketone which was used without purification.

A solution of 294 mg of chloromethyl ketone and 120 mg of thioacetamide in 5 mls of DMF was heated on a steam bath for 8 hours. The reaction was then poured onto H_2O and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated to give 260 mg crude product. Purification on silica gel with CH_2Cl_2/ethyl acetate gave 90 mg of the title product, M.P. 81-82°C.

PREPARATION 44

1-(3-Hydroxy-4-methoxyphenyl)-1H-imidazo[4,5-c]pyridine

A mixture of 5.7 g of 3-nitro-4-chloropyridine, 3 g of $NaHCO_3$ and 5 g of 5-amino-2-methoxyphenol in 100 ml of ethanol was stirred at room temperature overnight. The ethanol was evaporated and the residue slurried with hot THF to dissolve

the product. Evaporation of the THF gave 8.7 g of the nitro product used without purification.

The nitro compound from above (8.7 g) was reduced with H_2 and Pd/C on a Parr shaker during 5 hours. The reaction was filtered over celite and evaporated to give 8.2 g of the amine product.

A solution of 2.7 g of the amino pyridine from above in 75 ml of formic acid containing 1.7 g of ethyl formate was heated at 100°C for 8 hours. The volatiles were evaporated and the residue was treated with methanolic NaOH at 100°C for 2 hours. The reaction was cooled and the pH adjusted to 7.0 with 1N HCl. The resulting solid was filtered and dried to give 2.05 g of product. M.P.: 231-233°C.

PREPARATION 45

1-(5-Bromo-2-methoxyphenoxy)-
5-(4-fluorophenyl)pentane

(a) Preparation of 6-(4-fluorophenyl)-1-hexene

A suspension of 6-bromo-1-hexene (10 g), magnesium (1.5g), and iodoethane (1 drop) in anhydrous tetrahydrofuran was heated at reflux until all of the magnesium dissolved. The resulting Grignard reagent was cooled to about 0°C and was treated with a 1M solution of $ZnCl_2$ in ether (67 ml), and the mixture was allowed to warm to room temperature over 30 minutes. Tetrakis(triphenylphosphine)palladium (0) (3.5 g) and 4-bromofluorobenzene (6.73 ml) were added to the reaction and the mixture was heated to reflux for 1 hour. The mixture was cooled to room temperature, concentrated in vacuo, diluted with hexane, filtered and concentrated once more in vacuo. Chromatography on a silica gel column eluting with ether-hexane (0-5%) afforded 5 g of a colorless oil.

(b) Preparation of 5-(4-fluorophenyl)pentanal

The above oil (2.5 g) was dissolved in 1:9 methanol-methylenechloride (50 ml), cooled to about -78°C and treated with ozone gas until the mixture became light blue. At this time ozone addition was ceased and the mixture was purged with nitrogen gas. Triphenylphosphine (5 g) was added and the mixture was allowed to stand at room temperature over 24 hours. The reaction mixture was concentrated in vacuo, diluted with ether, filtered and concentrated once more in vacuo. Chromatography on a silica gel column eluting with ethyl acetate-hexane (10-20%) gave 1.3 g of aldehyde as a colorless oil.

(c) Preparation of 5-(4-fluorophenyl)pentanol

The above aldehyde (1.3 g) was dissolved in methanol (20 ml) at about 0°C and treated with sodium borohydride (1.0 g). After 10 minutes the mixture was quenched with saturated aqueous ammonium chloride, and was extracted with ether. The combined organics were washed with water followed by brine, dried over sodium sulfate, filtered and concentrated in vacuo. Filtration through silica gel gave 1.2 g as a colorless oil.

(d) Preparation of the title compound

1-(5-Bromo-2-methoxyphenoxy)-5-(4-fluorophenyl)pentane was prepared from 5-bromoguaiacol and 5-(4-fluorophenyl)pentanol as in Preparation 11. M.P.: 46-47°C.

PREPARATION 46

1-(5-Bromo-2-methoxyphenoxy)-
4-(4-fluorophenoxy)butane

(a) Preparation of 4-(4-fluorophenoxy)-1-butene

A solution of 4-bromo-1-butene (4.0 g), 4-fluorophenol (3.0 g), potassium carbonate (3.8 g) and acetone (75 ml) was heated at reflux over 16 hours. The mixture was then concentrated in vacuo, diluted with ether, washed with water followed by 1N sodium hydroxide, dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on a silica gel column eluting with 25% ethyl acetate-hexane afforded 1.6 g of a colorless oil.

(b) Preparation of 1-bromo-4-(4-fluorophenoxy)butane

Anhydrous HBr was bubbled through a mixture of the above oil (1.6 g) and benzoyl peroxide (0.136 g) in petroleum ether (60 ml) kept below 15°C using an ice-bath. After 30 minutes the system was purged with nitrogen, diluted with petroleum ether (50 ml) and washed with saturated aqueous sodium bicarbonate and brine. The mixture was then dried over sodium sulfate, filtered and concentrated in vacuo. Chromatography on a silica gel column eluting with ethyl acetate-hexane (5-10%) afforded 2.08 g as a colorless oil.

(c) Preparation of the title compound

A mixture of the above oil (2.08 g), 5-bromoguaiacol (1.71 g), potassium carbonate (3.5 g) and dimethylformamide (35 ml) was stirred at about 80°C over 3 hours. The mixture was cooled to room temperature, poured into water (250 ml) and extracted with 20% ethyl acetate-hexane. The combined organics were washed with brine, dried over sodium sulfate and concentrated in vacuo. Chromatography on a

silica gel column eluting with 25% ethyl acetate-hexane afforded 2.27 g of a white crystalline solid. M.P.: 44-47°C.

PREPARATION 47

4-Methoxy-3-(5-phenylpentoxy)benzoic acid

To a magnetically stirred solution of 4-methoxy-3-(5-phenylpentoxy)-benzaldehyde (9.90 grams, 33.2 mmols) and 2-methyl-2-butene (56.2 ml, 530 mmoles) in tert-butanol (300 ml) was added a solution of sodim chlorite (24.0 grams) and sodium phosphate monobasic (24.0 grams) in water (200 ml) over 10 minutes. After stirring vigorously for about 30 minutes the mixture was concentrated under reduced pressure and acidified to pH2 with 6N HCl. The precipate was filtered and dried to give 9.4 grams of a white solid, MS m/z [M^+]314.

PREPARATION 48

4-[(5-Bromo-2-methoxy)phenoxy]butanoic acid ethyl ester

A mixture of 15.0 g (0.0740 mol) of 2-methoxy-4-bromophenol, 17.4 g (0.0890 mol) of ethyl 4-bromobutyrate, 20.5 g (0.148 mol) or K_2CO_3, and 200 ml of DMF was stirred at about 80°C was continued for about 16 h. The combined ether extracts were washed with brine (1 x 300 ml), dried ($MgSO_4$), and evaporated to give 26.0 g of an orange oil. Purification by flash chromatography using an ethyl acetate-hexane (1:4) eluant gave 19.7 g (84%) of the title compound as a clear oil (R_f 0.5 EtOAc-hexane, 3:7). ^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, t, J=7), 2.09-2.18 (2H, m), 2.51 (2H, t, J=7), 3.82 (3H, s), 4.03 (2H, t, J=7), 4.13 (2H, q, J=7), 6.72 (1H, d, J=8), 6.97-7.08 (2H, m).

PREPARATION 49

4-[(5-Bromo-2-methoxy)phenoxy]butanal

A solution of 1.50 g (4.72 mmol) of the compound of Preparation 48 in 15 ml of dry THF was chilled to about -78°C and was treated dropwise with 7.08 ml (7.08 mmol) of a solution of 1.0 M diisobutylaluminum hydride in hexane at such a rate that the reaction temperature did not rise above -60°C. After stirring an additional 0.5 h, 5 ml of methanol was added dropwise. After the exotherm had subsided, 25 ml of IN HCl was added and the mixture was allowed to warm room temperature. The THF and methanol was removed by evaporation, and the residue was diluted with 150 ml of IN HCl and was extracted with EtOAc (2 x 100 ml). The combined extracts were washed with saturated $NaHCO_3$ solution (2 x 100 ml), brine (1 x 100 ml), dried ($MgSO_4$), and evaporated to give 1.25 g of a clear oil. Purification by flash chromatography using an EtOAc-hexane eluant (3:7) afforded 523 mg (41%) of the title compound as a clear oil

(R_f 0.5 EtOAc-hexane, 1:1). ^{1}H-NMR δ 2.10-2.20 (2H, m), 2.68 (2H, t, J=6), 3.80 (3H, s), 4.00 (2H, t, J=6), 6.71 (1H, d, J=9), 6.95-7.04 (2H, m), 9.82 (1H, s).

PREPARATION 50

4-(5-Bromo-2-methoxy)phenoxy-1-(3,4-dimethyl)phenyl-1-butanol

A solution of 176 mg (0.952 mmol) of 4-bromo-*o*-xylene in 5 ml of dry THF was chilled to about -78°C and was treated dropwise with 0.322 ml (0.805 mmol) of a 2.5 M solution of *n*-BuLi in hexane. When the exotherm had subsided, the mixture was stirred an additional 10 min, and a solution of 200 mg (0.732 mmol) of the compound of Preparation 49 in 5 ml of THF was added. The mixture was stirred an additional 20 min and was quenched by the addition of saturated aqueous NH_4Cl solution. After warming to room temperature, the THF was removed by evaporation and the residue was diluted to 100 ml with water and was extracted with EtOAc (2 x 100 ml). The extracts were combined, dried (Na_2SO_4), and evaporated to give 400 mg of a clear oil. Purification by flash chromatography using an EtOAc-hexane eluant (3:7) afforded 172 mg (62%) of the title compound as an oil (R_f 0.4 EtOAc-hexane). ^{1}H NMR ($CDCl_3$): δ 1.81-1.87 (4H, m), 2.22 (3H, s), 2.23 (3H, s), 3.89 (3H, s), 3.96-4.01 (2H, m), 4.60-4.69 (1H, m), 6.66 (1H, d, J=9), 6.87-7.08 (5H, m).

PREPARATION 51

4-Carbomethoxy-2-methylphenylboronic acid

To a solution of 50.0 g (0.232 mol) of 4-bromo-3-methylbenzoic acid in 500 ml of dry THF at about -78°C was added dropwise 300 ml (0.511 mol) of a 2.5 M solution of *n*-BuLi in hexane over a period of about 0.5 h. After 20 min. of additional stirring at about -78°C, 64.0 g (0.278 mol) of tributylborane was added dropwise. The mixture was stirred an additional 3 h at about -78°C, and, following removal of the ice bath, 500 ml of IN HCl solution was added carefully. The mixture was stirred for about 16 h at room temperature and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 50 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was triturated in hexane and 16 g of a white solid was removed by filtration. The mother liquor was concentrated and was purified by flash chromatography using an EtOAc-hexane eluant (3:7 to 1:1) to give 4.00 g of crude 4-carboxy-2-methylphenylboronic acid; (R_f 0.1 EtOAc-hexane, 1:1). This material was dissolved in 60 ml of thionyl chloride and was refluxed for 1 h. The excess thionyl chloride was removed by distillation under reduced pressure, and the oily residue was diluted with 100 ml of methanol. The mixture was stirred for about 16 h at room

temperature and the methanol was removed by evaporation. The residue was purified by flash chromatography using an EtOAc-hexane eluant (3:7 to 1:1) to afford 2.35 g (4%) of the title compound as a white solid (R_f 0.35 EtOAc-hexane, 1:1). ^{1}H-NMR (DMSO-d^6): δ 2.68 (3H, s), 3.81 (3H, s), 7.66-7.72 (2H, m), 7.93 (1H, d, J=8).

PREPARATION 52

4-[3-[4-(3,4-Dimethylphenyl)-4-hydroxy]butyloxy-4-methoxy]phenyl-3-methylbenzoic acid methyl ester

To a solution of 170 mg (0.448 mmol) of the compound of Preparation 49 in 4 ml of toluene was added 17 mg of tetrakistriphenylphosphinepalladium, a solution of 82 mg (0.448 mmol) of the compound of Preparation 51 in 2 ml of EtOH, and 0.670 ml of saturated aqueous solution of Na_2CO_3. The resulting mixture was heated to reflux for about 4 h. The mixture was partially evaporated to remove toluene and ethanol, and the residue was diluted with EtOAc and was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give 228 mg of a brown oil. Purification by flash chromatography with an ETOAc-hexane eluant (3:7) afforded 72 mg (36%) of the title compound as a foam (R_f 0.45 EtOAC-hexane 1:1). ^{1}H-NMR: δ 1.82-1.97 (4H, m), 2.20 (3H, s), 2.21 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.97-4.08 (2H, m), 4.63-4.72 (1H, m), 6.73-7.25 (6H, m), 7.82 (1H, d, J=8), 7.88 (1H, s).

PREPARATION 53

4-Bromo-4-methoxy-3-[(4-aminophenyl)butyloxy]benzene

A mixture of 298 mg (1.09 mmol) of the compound of Preparation 49, 11 mg (1.20 mmol) of aniline, and 5 ml of MeOH was stirred at room temperature for about 1 h. The mixture was chilled to about 0°C and was treated with 46 mg (1.22 mmol) of $NaBH_4$. After stirring for about 2 h at about 0°C, excess IN HCl was added and the mixture was partially evaporated to remove MeOH. The residue was overlayed with EtOAc, and the aqueous layer was basified to pH 8. The organic layer was separated and was combined with two EtOAc extracts of the aqueous layer. The combined organic extracts were dried (Na_2SO_4) and evaporated to give an oil, which was purified by flash chromatography using an EtOAc-hexane eluant (1:4) to afford 135 mg (35%) of the title compound as an oil (R^f 0.4 EtOAc-hexane, 3:7). ^{1}H-NMR δ; 1.77-1.94 (4H, m), 3.19 (2H, t, J=6), 3.81 (3H, s), 4.00 (2H, t, J=6), 6.58-7.16 (8H, m).

PREPARATION 54

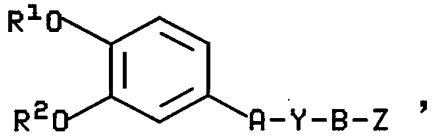
4-[3-[(4-Aminophenyl)butyloxy]-4-methoxy]phenyl-3-methylbenzoic acid methyl ester

Following the same procedures in Preparation 52, 1.88 mg (0.536 mmol) of the compound of Preparation 53 and 109 mg (0.590)mmol) of the compound of Preparation 51 were coupled to give 193 mg (86%) of the title compound. Purification was performed by flash chromatography using an EtOAc-hexane (1:4) eluant. ^{1}H-NMR δ 1.80-2.02 (4H, m), 2.32 (3H, s), 3.21 (2H, t, J=7), 3.91 (s, 3H), 3.93 (s, 3H), 4.06 (2H, t, J=6), 6.60-7.30 (9H, m), 7.87 (1H, d, J=8), 7.93 (1H, s).

CLAIMS

What is claimed is:

1. A compound of the formula



(I)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically acceptable salts thereof wherein

R^1 is selected from the group consisting of methyl, ethyl, difluoromethyl and trifluoromethyl;

R^2 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, alkoxyalkl having 3 to 7 carbons in the alkoxy portion and 2 to 4 carbons in the alkyl portion, phenoxyalkyl having 2 to 6 carbons in the alkyl portion, $(C_3\text{-}C_7)$cycloalkyl, $(C_6\text{-}C_9)$polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion, phenylaminoalkyl having 2 to 6 carbons in the alkyl portion and the amino may be optionally substituted with $(C_1\text{-}C_4)$ alkyl and indanyl,

where the alkyl portion of said alkyl, phenoxyalkyl, cycloalkyl, polycycloalkyl, phenylalkyl and indanyl may optionally be substituted with one or more fluorine atoms, -OH or $(C_1\text{-}C_4)$alkoxy,

and the aryl portion of said phenylalkyl, phenoxyalkyl and indanyl may optionally be substituted with $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or halogen;

A and B are independently selected from the group consisting of a covalent bond, optionally substituted $(C_1\text{-}C_5)$alkylene, optionally substituted $(C_2\text{-}C_5)$alkenyl and optionally substituted phenylene,

where said optionally substituted alkylene may be monosubstituted and each substituent is selected from the group consisting of oxo, $(C_1\text{-}C_4)$alkoxy, CO_2R^6 and hydroxy,

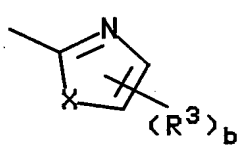
said optionally substituted alkenyl may be monosubstituted with $(C_1\text{-}C_4)$alkoxy or CO_2R^6, and

said optionally substituted phenylene may be monosubstituted with $(C_1\text{-}C_4)$alkoxy, CO_2R^6 or hydroxy,

wherein R^6 is hydrogen or $(C_1\text{-}C_4)$alkyl;

Y is selected from the group consisting of a covalent bond, O, NR^6 and S wherein R^6 is as defined above;

Z is selected from the group consisting of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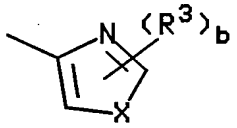
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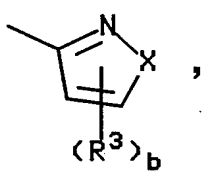
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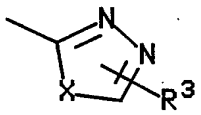
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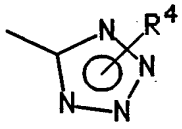
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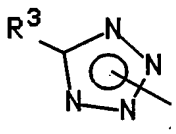
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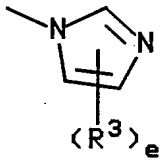
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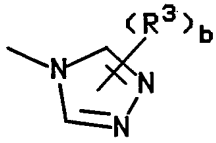
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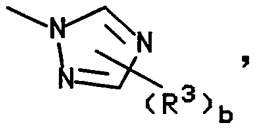
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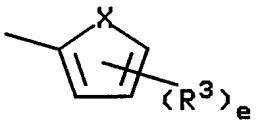
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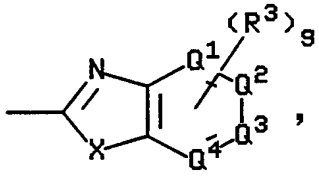
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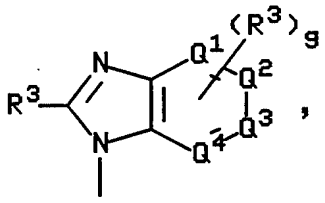
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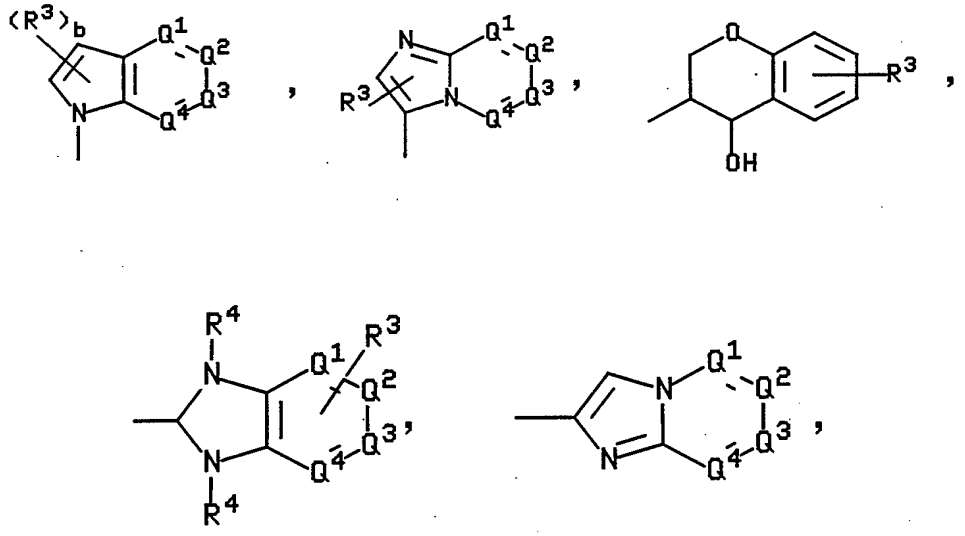

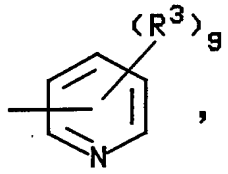
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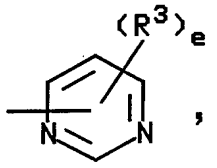
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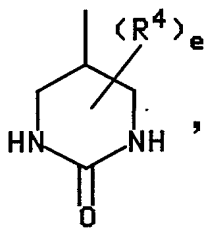
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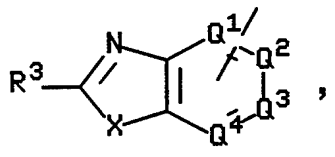
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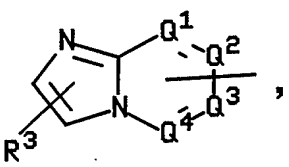
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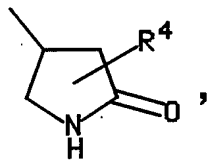
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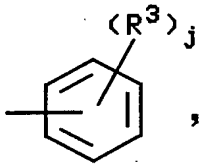
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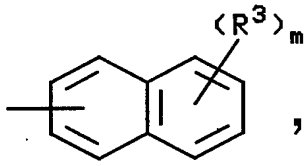
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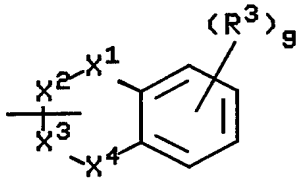
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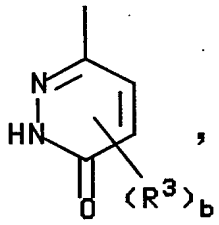
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where Q^1, Q^2, Q^3, and Q^4 are independently N, CH or, when also bonded to B, C and provided that at least two of Q^1, Q^2, Q^3, and Q^4 are not N;

X is selected from the group consisting of O, NR^4 and S;

and X^1, X^2, X^3 and X^4 are independently selected from the group consisting of O, NR^4, S, C=O, CH_2 and, when also bonded to B, CH;

b is an integer from 1 to 2;

e is an integer from 1 to 3;

g is an integer from 1 to 4;

j is an integer from 1 to 5;

m is an integer from 1 to 7;

each R^3 is independently selected from the group consisting of hydrogen, halogen, $(C_1$-$C_6)$alkyl, $CH(R^7)CO_2R^4$, $(C_1$-$C_6)$alkoxy, CO_2R^4, $CONR^4R^5$, CONHOH, $CH_2NR^4R^5$, NR^4R^5, nitro, hydroxy, CN, SO_3H, phenylalkyl having 1 to 4 carbons in the alkyl portion, $SO_2NR^4R^5$, $N(SO_2R^8)_2$ and $NHSO_2R^8$,

where R^4 for each occurrence is independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, phenyl optionally substituted with $(C_1$-$C_4)$alkyl or halogen, $CH(R^7)CO_2R^6$, $(C_3$-$C_7)$cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion and dialkylaminoalkyl having a total of 5 carbons in the dialkylamino portion and having 2 to 5 carbons in the alkyl portion where R^6 is as defined above,

R^5 for each occurrence is independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, phenylalkyl having 1 to 4 carbons in the alkyl portion, phenyl, pyridyl, pyrimidyl, thiazolyl and oxazolyl,

or R^4 and R^5 are taken together with the nitrogen to which they are attached and form an optionally substituted saturated or unsaturated 5- or 6-membered ring, a saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms, or a quinoline ring optionally substituted with fluoro,

where said optionally substituted saturated or unsaturated 5- or 6-membered ring may be mono- or di-substituted and each substituent is independently selected from the group consisting of alkyl having 1 to 4 carbons, CO_2R^7 wherein R^7 is as defined below, $CONH_2$, $CON(CH_3)_2$, oxo, hydroxy, NH_2 and $N(CH_3)_2$, and said saturated or unsaturated 6-membered heterocyclic ring containing two heteroatoms has the second heteroatom selected from the group consisting of O, S, NH, NCH_3, $NCOCH_3$ and NCH_2Ph;

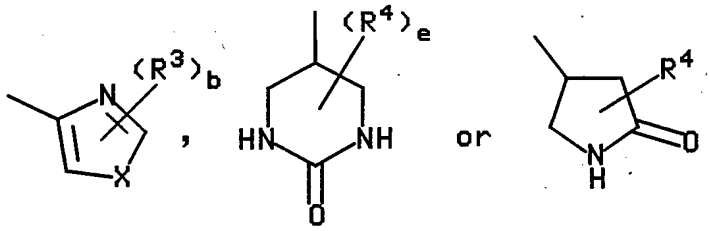
R^7 for each occurrence is independently selected from the group consisting of hydrogen and $(C_1$-$C_4)$alkyl;

and R^8 is selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, phenyl and phenyalkyl having 1 to 4 carbons in the alkyl portion;

with the proviso that:

when R^1 is methyl or ethyl; R^2 is $(C_7$-$C_9)$polycycloalkyl or indanyl; A, B and Y are covalent bonds; X is N; and R^3 is hydrogen;

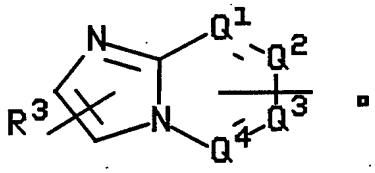
then Z is not



and with the further proviso that:

when R^1 is methyl or ethyl; R^2 is $(C_7\text{-}C_9)$polycycloalkyl or indanyl; A, B and Y are covalent bonds; Q^1, Q^2, Q^3, and Q^4 are CH or, when bonded to B, C; and R^3 is hydrogen;

then Z is not



2. A compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein

R^1 is selected from the group consisting of methyl and difluoromethyl;

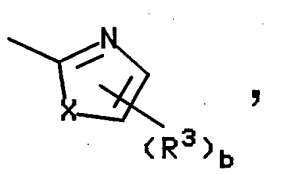
R^2 is selected from the group consisting of $(C_3\text{-}C_7)$cycloalkyl, $(C_6\text{-}C_9)$polycycloalkyl, phenylalkyl having 1 to 8 carbons in the alkyl portion and phenoxyalkyl having 2 to 6 carbons in the alkyl portion;

A is selected from the group consisting of a covalent bond, $(C_1\text{-}C_5)$alkylene and $(C_2\text{-}C_5)$alkenyl;

B is selected from the group consisting of a covalent bond, phenylene optionally substituted with $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_5)$alkylene and $(C_2\text{-}C_5)$alkenyl;

Y is selected from the group consisting of a covalent bond, O and NR^6;

Z is selected from the group consisting of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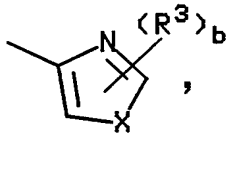
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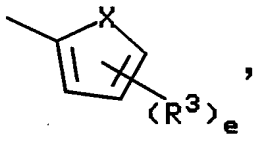
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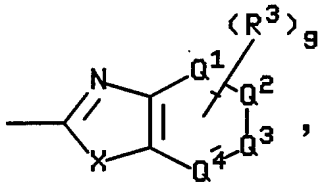
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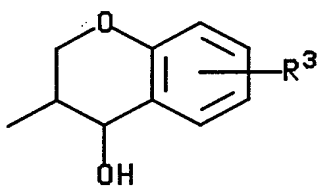
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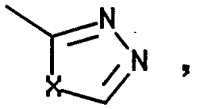
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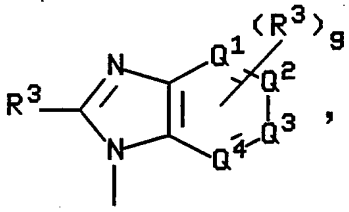
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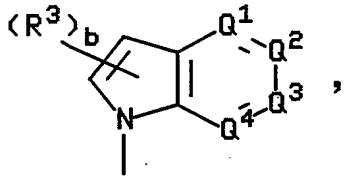
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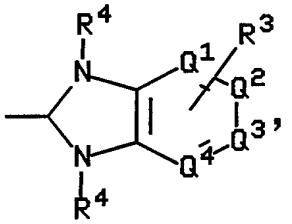
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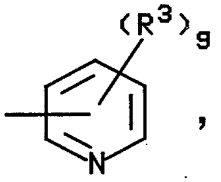
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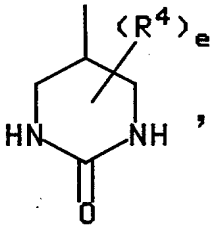
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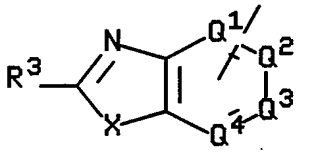
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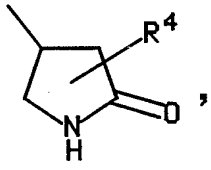
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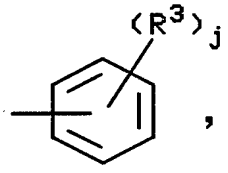
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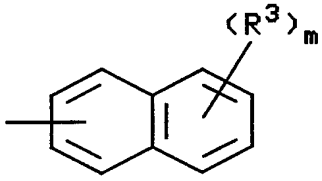
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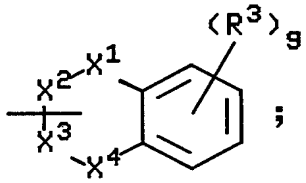
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each R^3 is independently selected from the group consisting of hydrogen, halogen, $(C_1$-$C_6)$alkyl, $CH(R^7)CO_2R^4$, $(C_1$-$C_6)$alkoxy, CO_2R^4, $CONR^4R^5$, nitro, hydroxy, $N(SO_2R^8)_2$ and $NHSO_2R^8$,

where R^4 for each occurrence is independently selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl and

R^5 is selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl.

3. A compound or a pharmaceutically acceptable salt thereof according to claim 2, wherein

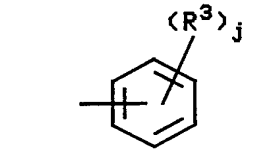
R^2 is selected from the group consisting of $(C_3$-$C_7)$cycloalkyl, $(C_6$-$C_9)$polycycloalkyl and phenylalkyl having 1 to 8 carbons in the alkyl portion;

A is selected from the group consisting of a covalent bond and methylene;

B is selected from the group consisting of a covalent bond, methylene and phenylene;

Y is selected from the group consisting of a covalent bond and O; and

Z is selected from the group consisting of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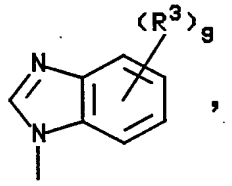
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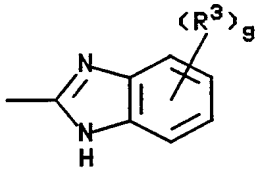
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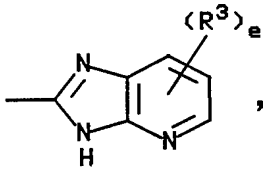
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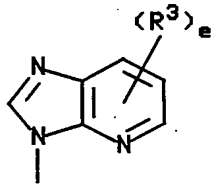
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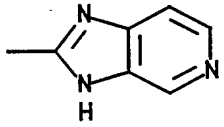
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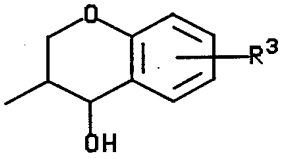
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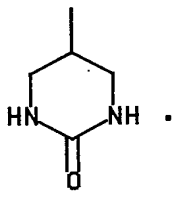
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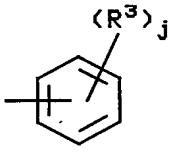
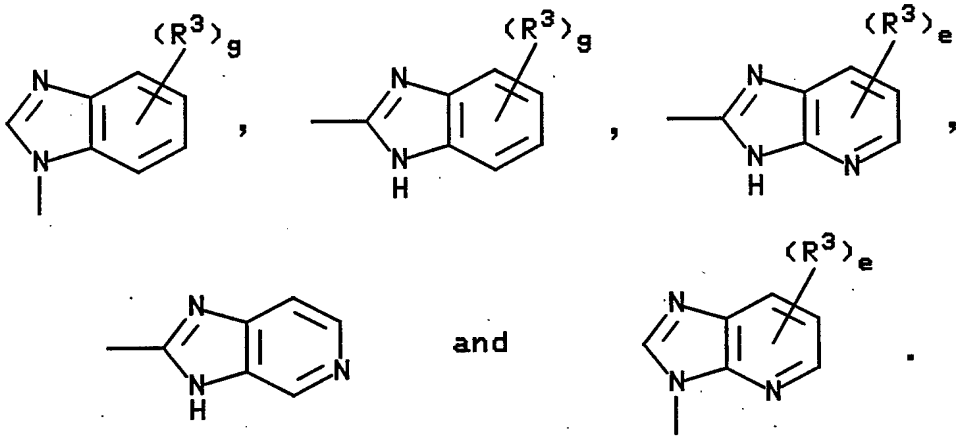
4. A compound or a pharmaceutically acceptable salt thereof according to claim 3, wherein A, B and Y are a covalent bond; and Z is  .

5. A compound or a pharmaceutically acceptable salt thereof according to claim 3, wherein A, B and Y are a covalent bond; and Z is selected from the group consisting of



and

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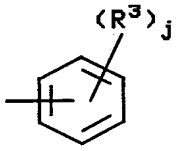
6. A compound or a pharmaceutically acceptable salt thereof according to claim 3 wherein

A is methylene;

B is a covalent bond;

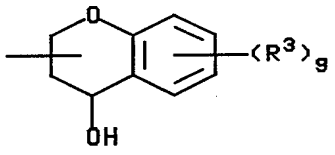
Y is O; and

Z is  .

7. A compound or a pharmaceutically acceptable salt thereof according to claim 3 wherein

A is methylene;

B and Y are a covalent bond; and

Z is 

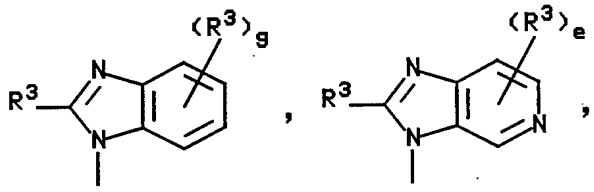
8. A compound or a pharmaceutically acceptable salt thereof according to claim 2 wherein

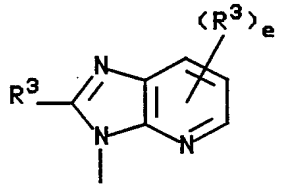
A is methylene;

B is phenylene;

Y is O; and

Z is selected from the group consisting of



and 

9. A pharmaceutical composition comprising an amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1 and a pharmaceutically acceptable diluent or carrier.

10. A method of inhibiting phosphodiesterase IV in a mammal in need thereof which comprises administering to said mammal a phosphodiesterase IV inhibiting amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1.

11. A method of treating an inflammatory condition in a mammal which comprises administering to said mammal an antiinflammatory amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1.

12. A method of treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis or shock in a mammal which

comprises administering to said mammal an effective amount of a compound or a pharmaceutically acceptable salt thereof according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/10228

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C65/21 A61K31/085 A61K31/19 A61K31/235 C07C69/76
C07C205/35 C07C205/57 C07C311/02 C07C311/51 C07C235/42
C07C235/34 C07C217/58 C07C217/80 C07C219/14 C07C255/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 19594 (SMITH KLINE BEECHAM) 12 November 1992 see page 6, line 6 - line 23; claim 1 ---	1,9
X	EP,A,0 511 865 (AMERICAN HOME PRODUCTS) 4 November 1992 see page 3, line 1 - line 41; claim 1 ---	1,9
X	WO,A,92 06963 (BYK GULDEN LOMBERG) 30 April 1992 see claims 1,8 ---	1,9
X	WO,A,84 04521 (BYK GULDEN LOMBERG) 22 November 1984 see page 3, line 29 - line 35; claim 1 ---	1,9
X	WO,A,87 06576 (PFIZER) 5 November 1987 see page 25, line 1 - line 20; claim 1 ---	1,9
	-/--	

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 March 1994	30. 03. 94

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 93/10228

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C271/02 C07C259/10 C07D213/79 C07D239/10 C07D401/14
C07D401/06 C07D207/26 C07D311/22 C07D279/16 C07D237/14
C07D471/04 C07D235/06 C07D333/38 C07D257/04 C07D209/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 428 313 (PFIZER) 22 May 1991 see claims 1,7 ---	1,9
X	EP,A,0 428 302 (PFIZER) 22 May 1991 see claims 1,13 ---	1,9
X	CHEMICAL ABSTRACTS, vol. 115, no. 15, 1991, Columbus, Ohio, US; abstract no. 158680z, G. WANG ET AL. 'A convinient method for the conversion of alpha-tetralones to aryl acetates' page 891 ; see abstract and 12th collective index, page 57274, column 3, lines 87-91 & SYNTH. COMMUN. 1991, 21(8-9), 989-96 --- -/--	1

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search
18 March 1994

Date of mailing of the international search report

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Fax (+31-70) 340-3016

Authorized officer
Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 93/10228

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D277/32 C07D277/22 C07D277/64 C07D513/04 C07D498/04
C07D285/12 C07D233/60 C07D231/12 C07D235/18 C07D233/90
A61K31/16 A61K31/325 A61K31/275 A61K31/135 A61K31/35

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 19, 1990, Columbus, Ohio, US; abstract no. 172319h, M. AKASU ET AL. 'Anticancer agents containing 1-benzylisoquinolines' page 80 ; see abstract & JP,A,01 233 221 (KAKEN) 19 September 1989 ---	1,9
X	WO,A,92 06085 (SMITH KLINE & FRENCH) 16 April 1992 see claim 10 and examples 12,24,29,35,43 -----	1

☐ Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 93/10228

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/38 A61K31/395 //(C07D471/04,235:00,221:00), (C07D513/04,277:00,221:00),(C07D498/04,263:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

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INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/US 93/ 10228

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 10-12 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
On grounds of Articles 6 and 17.2a(ii) of the PCT (conciseness of claims) and of the Guidelines for Examination in the EPO, Part B, Chapter III, 2.2 (economic reasons) the search has been based on the preparation examples disclosed in the description.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Internal Application No
PCT/US 93/10228

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

ormation on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9206085		JP-T- 6501254	10-02-94

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [5] :
C07D 519/00, 501/46, A61K 31/545

A1

(11) International Publication Number: **WO 94/29321**

(43) International Publication Date: 22 December 1994 (22.12.94)

(21) International Application Number: PCT/KR94/00061

(22) International Filing Date: 2 June 1994 (02.06.94)

(30) Priority Data:
1993/10188 5 June 1993 (05.06.93) KR

(71) Applicant: CHEIL FOODS & CHEMICALS INC. [KR/KR]; 150, Taepyungro 2-ga, Chung-ku, Seoul 100-102 (KR).

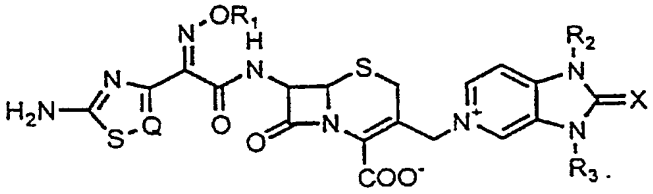
(72) Inventors: KIM, Choong, Sup; Changmi Apartment 12-306, Shincheon-dong, Songpa-ku, Seoul 138-240 (KR). AHN, Yang, Soo; Jukong Apartment 912-408, Myungil-dong, Kangdong-ku, Seoul 134-070 (KR). JUNG, Kang, Yeoun; 412-2, Yeokbuk-ri, Yongin-eub, Yongin-kun, Kyonggi-do 449-800 (KR). YUN, Rok, Lim; Hanshin Apartment 105-310, Inkye-dong, Paldal-ku, Suwon-shi, Kyonggi-do 442-070 (KR). PARK, Seong, Yong; 370-20, Yeonnam-dong, Mapo-ku, Seoul 121-240 (KR). YOON, Yeo, Hong; 609-10, Kongreung-dong, Nowon-ku, Seoul 139-240 (KR). LEE, Keon, Ho; 502-1601, Eunha Maeul, Choong-dong, Wonmi-ku, Bucheon-shi, Kyonggi-do 421-020 (KR). LYU, Chun, Seon; 614-232, Bangwha 2-dong, Kangseo-ku, Seoul 157-222 (KR). LEE, Kwang, Ho; Shinsigazi Apartment 405-1904, Mok-dong, Yangcheon-ku, Seoul 158-050 (KR).

(74) Agent: LEE, Kuiy, Dong; 114-31, Uni-dong, Chongro-ku, Seoul 110-350 (KR).

(81) Designated States: CN, JP, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NOVEL CEPHEM COMPOUNDS



(I)

(57) Abstract

The present invention relates to novel cephem compounds having formula (I) wherein Q is a carbon or nitrogen atom; X is an oxygen atom, or a nitroalkylenyl or cyanoimine group, with the proviso that X cannot be an oxygen atom when Q is a carbon atom; R_1 is a hydrogen atom, or a lower alkyl group, or a lower alkyl group which may be substituted by fluoro, or by a carboxylic group or an inorganic cation salt thereof; and R_2 and R_3 independently are a hydrogen atom or a lower alkyl group; or pharmaceutically acceptable salts thereof. The compounds of the present invention have potent antibacterial activities against gram-negative bacteria, especially *Pseudomonas*, and a longer half-life than conventional cephem compounds.

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NOVEL CEPHEM COMPOUNDS

TECHNICAL FIELD

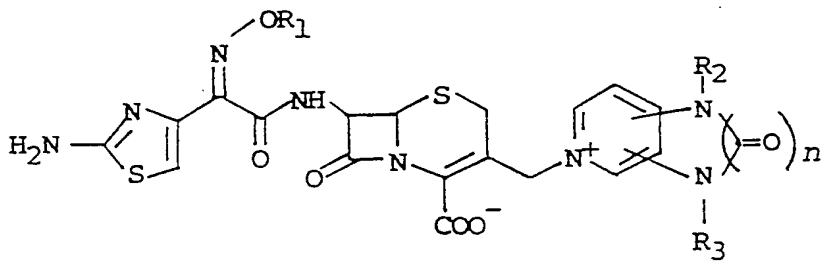
The present invention relates to novel cephem compounds and pharmaceutically acceptable salts thereof having potent antibacterial activities against gram-negative bacteria and an extended duration of action.

BACKGROUND ART

Since the first synthesis of cephem compounds in which the cephem nucleus has a carboxylic group at 4-position and a substituted amino group at 7-position, an extensive investigation has been made to develop a novel structure of cephem derivatives having more potent antibacterial activities and a broad antibacterial spectrum.

As prior art references which disclose such derivatives, U.S. Patent No. 4,152,432 to Heymes *et al.*; U.S. Patent No. 4,098,888 to Ochiai *et al.*; U.S. Patent No. 4,258,041 to O'Callaghan; U.S. Patent No. 4,748,172 to Katner; European Patent No. 0,318,552 to Katner; European Patent No. 0,164,944 to Bradbury; and European Patent No. 0,300,664 to Jung may be mentioned.

In most recent years, we have proposed, in our U.S. Serial No. 07/896,667, a class of novel compounds having the formula:

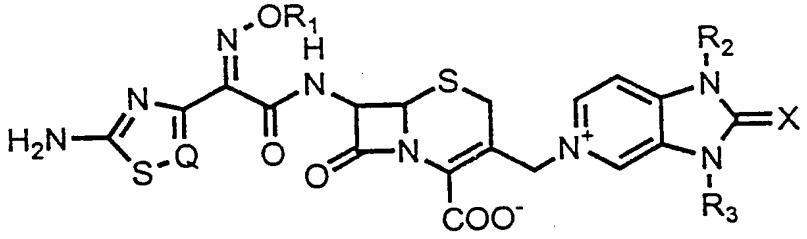


(I)

DISCLOSURE OF THE INVENTION

We have now found an another class of novel compounds which are neither described nor claimed in U.S. Serial No. 07/896,667. These novel compounds have been proven by the present invention to have potent antibacterial activities against gram-negative bacteria, especially *Pseudomonas*, and a significantly long duration of action.

Thus, in an aspect, the present invention provides novel cephem compounds having the formula:



(I)

wherein, Q is a carbon or nitrogen atom; X is an oxygen atom, or a nitroalkyl or cyanoimine group, with the proviso that X cannot be an oxygen atom when Q is a carbon atom; R_1 is a hydrogen atom, a lower alkyl group, or a lower alkyl group which may be substituted by fluoro, or by a carboxylic group or an inorganic cation salt thereof; and R_2 and R_3 independently are a hydrogen atom or a lower alkyl group; or pharmaceutically acceptable salts thereof.

As used herein, the term "lower alkyl" refers to alkyl groups having 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, *tert*-butyl, butyl, or pentyl, unless otherwise indicated.

Pharmaceutically acceptable salts of the compounds of the formula (I) include an inorganic cation salt, for example, an alkali metal salt (*e.g.*, sodium salt, potassium salt, *etc.*), an alkaline earth metal salt (*e.g.*, calcium salt, magnesium salt, *etc.*); an inorganic acid salt (*e.g.*, hydrochloride, hydrobromide, hydroiodide, sulfate, carbonate, bicarbonate, *etc.*); an organic acid salt (*e.g.*, maleate, lactate, tartarated, *etc.*); a sulfonate (*e.g.*, benzenesulfonate, methanesulfonate, paratoluenesulfonate, *etc.*); a salt with an amino acid such as arginine, lysine, glycine, *etc.*; and an amine

salt (*e.g.*, ammonium salt, trimethylamine salt, triethylamine salt, pyridine salt, procaine salt, picoline salt, *etc.*), and the like.

Particularly preferred specific compounds according to the invention are as set forth below:

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate; and

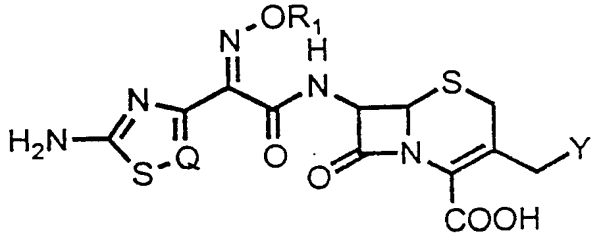
7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate.

The most preferred compounds of the invention are those in which Q is a nitrogen atom; X is an oxygen atom; R_1 is a hydrogen atom, a methyl, fluoromethyl

or carboxymethyl group; at least one of R_2 and R_3 is a hydrogen atom.

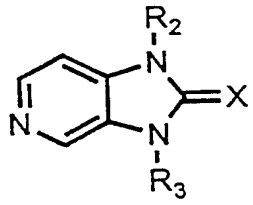
The compounds according to the present invention have a long duration of action (half-life) and exhibit potent antibacterial activities against gram-negative bacteria such as *Pseudomonas*.

The compounds of the formula (I) and pharmaceutically acceptable salts thereof can be prepared by reacting a compound having the formula (II):



(II)

wherein, Q and R_1 have the same meanings as defined above; and Y is a halogen atom or an acetoxy group;
with a compound having the formula (III):



(III)

wherein, X, R_2 and R_3 have the same meanings as defined above.

Preferably, the halogen atom may include chlorine, bromine or iodine, more preferably iodine.

According to the invention, a compound of the formula (II) is first silylated with a silylating agent in an aprotic organic solvent to protect the carboxy group at 4-position and the amino group at 7-position, of the cephem nucleus.

Such a silylating agent may include N,O-bis(trimethylsilyl)acetamide, N-

methyl-N-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-(trimethyl-silyl)trifluoroacetamide, and hexamethyldisilazane. As an appropriate aprotic organic solvent, there may be mentioned nitriles such as acetonitrile and propionitrile; alkyl halides such as chloroform, carbon tetrachloride and dichloromethane; ethers such as tetrahydrofuran and dioxane; amides such as N,N-dimethylformamide; esters such as ethylacetate and methylacetate; ketones such as acetone, methylethylketone and methylisobutylketone; sulfoxides such as dimethylsulfoxide; and aromatic hydrocarbon solvents such as benzene and toluene.

The silylated compound of the formula (II) is then reacted with trimethylsilyliodide (TMSI) at ambient temperature to give a compound of the formula (II) in which Y is iodine. This reaction is disclosed, for example, in U.S. Patent No. 4,266,049 to Bonjouklian and U.S. Patent No. 4,748,172 to Katner.

A compound of the formula (III), 2-oxoimidazo pyridine compound, may also be prepared by known methods [See: J. Chem. Soc. (B), 285(1966); J. Org. Chem. 33(6), 2543(1968); J. Org. Chem., 43(3), 393(1978); J. Heterocyclic Chem., 13, 601(1976); J. Heterocyclic Chem., 22, 1061(1985); Syn, Comn., 12(3), 213(1982); Bull. Chem. Soc. Jpn., 60, 1973(1987)], and is silylated with the same silylating agent as mentioned above in an anhydrous aprotic organic solvent.

The silylated 3-iodomethyl cephem compound of the formula (II) is then reacted with a compound of the formula (III) in an anhydrous aprotic solvent to give a silylated compound of the formula (I). Hydrolysis of the silyl group provides a compound of the formula (I) according to the present invention. The resulting compound of the formula (I) is isolated from the reaction mixture and purified by known methods such as extraction using organic solvents, crystallization, column chromatography, and so forth.

The compounds of the present invention may be formulated for administration in the form of an injection (*e.g.*, intravenous, intraperitoneal, intramuscular, or subcutaneous injection) in accordance with conventional methods known in the art. Alternatively, the compounds may be formulated into various kinds of dosage forms, for example, capsules, tablets, pills, solutions, suspensions, emulsions, suppositories, pastes, ointments, gels, creams, lotions, powders, and sprays.

Tablets, capsules, pills and granules can contain the active compound or compounds in combination with the customary excipients, such as fillers and extenders, for example, starches, lactose, sucrose, glucose, mannitol and silica; binders, for example, carboxymethyl-cellulose, alginates, gelatine and polyvinyl pyrrolidone; humectants, for example, glycerine; disintegrating agents, for example, agar-agar, calcium carbonate and sodium carbonate; absorption accelerators, for example, quaternary ammonium compounds; wetting agents, for example, cetyl alcohol or glycerine monostearate; adsorbents, for example, kaolin and bentonite; and lubricants, for example, talc, calcium stearate, and magnesium stearate.

Suppositories can contain, in addition to the active compound or compounds, customary aqueous or non-aqueous excipients, for example, polyethylene glycols, fats, for example, cacao fat, and higher esters (for example, a C_{14} alcohol with a C_{16} fatty acid), or mixtures of these substances.

Ointments, pastes, creams and gels can contain customary excipients, in addition to the active compound or compounds, for example, animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talc, and zinc oxide, or mixtures of these substances.

Powders and sprays can also contain customary excipients in addition to the active compound or compounds, for example, lactose, talc, silica, aluminum hydroxide, calcium silicate, and polyamide powders, or mixtures of these substances. Sprays can additionally contain customary propellants, for example, chlorofluorohydrocarbons.

Solutions and emulsions can contain customary excipients, in addition to the active compound or compounds, such as solvents, solubilizing agents, and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, especially cottonseed oil, groundnut oil, corn germ oil, olive oil, caster oil and sesame oil, glycerine, glycerineformal, tetrahydrofurfuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, or mixtures of these substances.

For parenteral administration, the solutions and emulsions can also be in sterile form, which is isotonic with blood.

Suspensions can contain customary excipients, in addition to the active compound or compounds, such as liquid diluents, for example, water, ethyl alcohol or propylene glycol, suspending agents, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol esters and sorbitan esters, microcrystalline cellulose, aluminum meta-hydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances.

BEST MODE FOR CARRING OUT THE INVENTION

The present invention will be described in greater detail by way of the following examples. The examples are presented for illustration purposes only and should not be construed as limiting the invention which is properly delineated in the claims.

Preparation 1: 2-(1H,3H)-Nitromethylen-yl-imidazo[4,5-c]pyridine

1 G of 1,1-bis(methylthio)-2-nitroethylene and 0.6 g of 3,4-diaminopyridine were placed into a 50 ml reaction vessel. To the mixture was added 20 ml of ethyl alcohol. The resulting dispersion was heated to an elevated temperature and stirred under reflux for 10 hrs, while trapping the methanethiol discharged into an aqueous 20 % NaCl solution. Thereafter, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel eluting with dichloroethane:methyl alcohol (2:1) to give 500 mg of the title compound.

IR (KBr, cm^{-1}): 3416; 1517; 1319.
NMR (DMSO-d_6): 7.5(1H, d); 8.2(1H, d); 8.7(1H, s); 7.4(1H, s).

Preparation 2: 2-(1H,3H)-Cyanoimine-imidazo[4,5-c]pyridine

2 G of dimethyl N-cyanodithioiminocarbonate and 1.34 g of 3,4-diaminopyridine were placed into a 100 ml reaction vessel. To the mixture was added 30 ml of acetonitrile. The resulting dispersion was heated to an elevated temperature and stirred under reflux for overnight, while trapping the methanthiol

discharged into an aqueous 20 % NaCl solution. After completion of the reaction, the precipitated solids were filtered out and dissolved in dichloroethane:methyl alcohol (2:1), and then separated by column chromatography on silica gel to give 1 g of the title compound.

IR (KBr, cm^{-1}): 2180; 1652; 1604; 1488.
NMR (DMSO-d_6): 7.2(1H, d); 8.2(2H, d); 8.3(1H, s).

Preparation 3: 2-(1H,3H)-Oxo-imidazo[4,5-c]pyridine

3 G of 3,4-diaminopyridine and 1.65 g of urea were added to 30 ml of dimethylformamide. The mixture was stirred under reflux for 6 hrs, allowed to cool to room temperature, and stirred further for 12 hrs to precipitate solids. The resulting solids were filtered out, and dissolved in methyl alcohol. The resulting solution was treated with active carbon, and concentrated under reduced pressure to give 3.1 g of the title compound as a white solid.

IR (KBr, cm^{-1}): 3125; 1717; 1630.
NMR (DMSO-d_6) : 8.14(1H, s); 8.10(1H, d); 6.97(1H, d).

Preparation 4: 1-Methyl-2(3H)-oxo-imidazo[4,5-c]pyridine

4.3 G of 4-methylamino-3-aminopyridine and 2.1 g of urea were added to 43 ml of dimethylformamide. The resulting mixture was stirred under reflux for 4 hrs, and then allowed to cool to room temperature. The resulting solids were filtered out, and dissolved in methyl alcohol under reflux. The solution was then cooled slowly to precipitate solids. The solution containing the precipitated solids were stirred further for 1 hr and filtered out to give 3.9 g of the title compound as a white solid.

IR (KBr, cm^{-1}): 2739; 1715; 1624.
NMR (DMSO-D_2O): 8.18(1H, s); 8.13(1H, d); 7.1(1H, d); 3.27(3H, s).

Example 1: 7-β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl-3-cephem-4-carboxylate

500 Mg of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxy-methyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane. The resulting suspension was added to 0.7 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 1 hr to effect silylation. To the silylated solution was added 0.38 ml of iodotrimethylsilane at 0 °C. The reaction mixture was stirred for 30 mins at room temperature. Thereafter, the mixture was concentrated, and then the concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran to produce a solution. Separately, 200 mg of 2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridine was dissolved in a mixture of 10 ml of acetonitrile and 0.79 ml of N,O-bis(trimethylsilyl)acetamide. The resulting solution was subjected to silylation for 1.5 hrs to give a silylated pyridine derivative. The derivative was added to the solution previously obtained, and the mixture was allowed to react at room temperature for 3 hrs. Then, to the reaction mixture was added a mixed solvent of 0.5 ml of methyl alcohol and 5 ml of acetonitrile to effect deprotection. The reaction mixture was stirred at 0 °C for 30 mins. The resulting solids were filtered out, dissolved in 10 ml of water while adjusting the pH to 6.5 with sodium bicarbonate, and then concentrated. The residue was purified by chromatography on silica gel with acetonitrile:water (4:1) to give 181 mg of the title compound.

IR (KBr, cm^{-1}): 3420; 1760; 1670; 1520; 1320.
NMR (DMSO-d_6): 3.14(1H, d); 3.52(1H, d); 3.76(3H, s); 5.17(1H, d); 5.30(1H, d), 5.71(1H, d), 5.79(1H, d); 6.69(1H, s); 7.11(2H, br), 8.17(1H, d); 8.45(1H, d); 9.01(1H, s), 9.53(1H, d).

Example 2: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate

500 Mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2- methoxyimino-acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane. To the resultant suspension was added 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoro-acetamide. The mixture was stirred at room temperature for 1 hr to effect silylation. To the silylated solution was added slowly

0.40 ml of iodotrimethylsilane at 0 °C. The reaction mixture was allowed to stand at room temperature, stirred for 30 mins, and then concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran to produce a solution. Separately, 202 mg of 2-(1H,3H)-nitro-methylen-yl-imidazo[4,5-c]pyridine was dissolved in a mixture of 10 ml of acetonitrile and 0.81 ml of N,O-bis(trimethylsilyl)acetamide. The resulting solution was subjected to silylation for 1.5 hrs to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was allowed to react at room temperature for 3 hrs. Then, to the reaction mixture was added a mixed solvent of 0.5 ml of methyl alcohol and 5 ml of acetonitrile to effect deprotection. The reaction mixture was stirred at 0 °C for 30 mins. Then, the resulting solids were filtered out and dissolved in 10 ml of water while adjusting the pH to 6.5 with sodium bicarbonate, and then concentrated. The residue was purified by column chromatography on silica gel with acetonitrile:water (4:1) to give 165 mg of the title compound.

IR (KBr, cm^{-1}): 3400; 2200; 1750; 1652; 1604.
NMR (DMSO-d_6): 3.14(1H, d); 3.49(1H, d); 3.78(3H, s); 5.14(1H, d); 5.19(1H, d), 5.70(1H, d), 5.80(1H, m); 7.64(1H, d), 8.0(2H, br); 8.75(1H, d); 9.21(1H, s).

Example 3: 7-β-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 700 mg of 7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 230 mg of 2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridine by the same procedure as described in Example 1.

Yield: 400 mg.
IR (KBr, cm^{-1}): 3401; 2180; 1749; 1652.
NMR (DMSO-d_6): 3.11(1H, d); 3.53(1H, d); 3.81(3H, s); 5.18(1H, d); 5.24(1H, d); 5.77(1H, d); 5.85(1H, m); 6.72(1H, s); 7.20(2H, br); 7.44(1H, d); 8.34(1H, d); 8.57(1H, s); 9.57(1H, d).

Example 4: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 500 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 200 mg of 2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 300 mg.
IR (KBr, cm^{-1}): 2412; 1750; 1653.
NMR (DMSO-d_6): 3.12(1H, d); 3.50(1H, d); 3.90(3H, s); 5.12(1H, d); 5.19(1H, d); 5.68(1H, d); 5.83(1H, m); 7.60(1H, d); 8.30(2H, br); 8.72(1H, d); 9.09(1H, s); 9.59(1H, d).

Example 5: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 500 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 160 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 300 mg
IR (KBr, cm^{-1}): 3400; 1750; 1690.
NMR (DMSO-d_6) : 3.1-3.5(2H, q); 4.0(3H, s); 5.1-5.7(2H, q); 5.8(1H, dd); 7.6(1H, s); 8.2(2H, s); 8.8(1H, d); 9.2(1H, s); 9.6(1H, d).

Example 6: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2-(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 500 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 160 mg of 1-methyl-2-(3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 300 mg
IR (KBr, cm^{-1}): 3401; 1750; 1660.
NMR (DMSO-d_6): 3.10(1H, d); 3.30(1H, d); 3.51(3H, s); 3.61(3H, s); 4.94(1H, d);

5.13(1H, d); 5.49(1H, d); 5.73(1H, m); 7.27(1H, d); 8.02(1H, s); 8.56(1H, d); 8.70(1H, s); 9.62(1H, d).

Example 7: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 500 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 190 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 200 mg
IR (KBr, cm^{-1}): 3300; 1764; 1651; 1612.
NMR (DMSO-d_6): 3.15(1H, d); 3.59(1H, d); 5.13(1H, d); 5.18(1H, d); 5.70(1H, d); 5.81(1H, d); 7.62(1H, d); 8.78(1H, d); 9.16(1H, d); 9.60(1H, d).

Example 8: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyimino-acetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3cephem-4carboxylate

The title compound was prepared by reacting 300 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4carboxylic acid with 250 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 150 mg.
IR (KBr, cm^{-1}): 3200; 1760; 1654; 1615.
NMR (DMSO-d_6): 3.28(1H, d); 3.37(1H, d); 4.50(2H, s); 5.12(1H, d); 5.71(1H, d); 5.85(1H, d); 7.46(1H, d); 8.37(1H, d); 8.70(1H, s); 9.47(1H, d).

Example 9: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyimino-acetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 700 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyiminoacetamido]-3-cephem-4-carboxylic acid

with 300 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 300 mg.

IR (KBr, cm^{-1}): 1761; 1652; 1613.

NMR (DMSO-d_6): 3.18(1H, d); 3.57(1H, d); 4.51(1H, s); 5.02(3H, s); 5.32(1H, d); 5.83(1H, d); 7.47(1H, d); 8.36(1H, d); 8.47(1H, s); 8.52(1H, d).

EXPERIMENT 1: In vitro Antibacterial Activity

In order to demonstrate the antibacterial activities of the compounds according to the present invention, minimum inhibitory concentration (MIC, μg/ml) for each compound synthesized in the above examples was determined in accordance with the method described in Chemotherapy, 29(1), p. 96 (1981).

As reference compounds, Cefotaxime (CTX), Ceftazidime (CAZ) and Cefpirome (CPR) were employed. The results are shown in Table 1 below.

Table 1

Minimum Inhibitory Concentration of the Present Compounds (MIC, μg/ml)

Compound / Strain	Ex. 1	Ex. 2	Ex. 3	Ex. 4
1. *S. pyogenes* ATCC 8668	0.007	0.013	0.004	0.007
2. *S. pyogenes* C4003	0.007	0.007	0.004	0.007
3. *S. faecalis* ATCC 29212	> 100.000	> 100.000	> 100.000	> 100.000
4. *S. aureus* Smith	0.780	3.130	1.560	3.130
5. *S. aureus* ATCC 29213	1.560	1.560	3.130	3.130
6. *S. aureus* C4036	1.560	3.130	3.130	3.130
7. MRSA C2208	> 100.000	> 100.000	> 100.000	> 100.000
8. *S. epidermidis* ATCC12228	0.780	1.560	0.780	1.560
9. *E. coli* C4002	0.100	0.100	0.050	0.100
10. *E. coli* ATCC 10536	0.050	0.050	0.013	0.050
11. *E. coli* ATCC 25922	0.100	0.100	0.050	0.100
12. *E. cloacae* C4008	0.050	0.050	0.013	0.050
13. *E. cloacae* C4009	0.200	0.200	0.025	0.050
14. *K. oxytoca* C4022	6.250	12.500	6.250	12.500
15. *K. pneumoniae* C1040	0.025	0.050	0.025	0.025
16. *K. pneumoniae* ATCC 10031	0.025	0.050	0.007	0.013
17. *P. mirabilis* ATCC 25933	0.100	0.100	0.025	0.025
18. *P. rettgeri* ATCC 9919	0.013	0.025	0.007	0.013
19. *S. typhimurium* C4045	0.100	0.200	0.025	0.050
20. *S. marcescens* C1052	0.200	0.200	0.050	0.050
21. *S. marcescens* ATCC 27117	0.100	0.200	0.025	0.050
22. *P. aeruginosa* C2027	6.250	6.250	6.250	6.250
23. *P. aeruginosa* ATCC10145	50.000	50.000	12.500	12.500
24. *P. aeruginosa* ATCC27853	50.000	> 100.000	6.250	25.000
25. *P. aeruginosa* C4070	> 100.000	> 100.000	12.500	12.500

Table 1 (Continued)

Compound / Strain	Ex. 5	Ex. 6	Ex. 7	Ex. 8
1. *S. pyogenes* ATCC 8668	0.013	0.007	0.100	0.100
2. *S. pyogenes* C4003	0.013	0.004	0.200	0.196
3. *S. faecalis* ATCC 29212	> 100.000	> 100.000	> 100.000	> 100.000
4. *S. aureus* Smith	1.560	3.130	6.250	3.130
5. *S. aureus* ATCC 29213	1.560	3.130	0.780	0.780
6. *S. aureus* C4036	1.560	3.130	1.560	1.560
7. MRSA C2208	> 100.000	> 100.000	> 100.000	> 100.000
8. *S. epidermidis* ATCC12228	0.780	1.560	3.130	1.560
9. *E. coli* C4002	0.007	0.025	6.250	3.130
10. *E. coli* ATCC 10536	0.004	0.007	0.025	0.013
11. *E. coli* ATCC 25922	0.013	0.025	0.050	0.050
12. *E. cloacae* C4008	0.002	0.013	0.100	0.013
13. *E. cloacae* C4009	0.007	0.013	0.100	0.013
14. *K. oxytoca* C4022	0.780	1.560	1.560	0.782
15. *K. pneumoniae* C1040	0.004	0.007	1.560	0.050
16. *K. pneumoniae* ATCC 10031	0.004	0.007	0.025	0.013
17. *P. mirabilis* ATCC 25933	0.025	0.025	0.100	0.050
18. *P. rettgeri* ATCC9919	0.007	0.007	0.500	0.025
19. *S. typhimurium* C4045	0.007	0.025	0.100	0.050
20. *S. marcescens* C1052	0.025	0.050	0.200	0.200
21. *S. marcescens* ATCC 27117	0.007	0.025	0.100	0.100
22. *P. aeruginosa* C2027	0.780	1.560	6.250	3.130
23. *P. aeruginosa* ATCC10145	1.560	1.560	12.500	3.130
24. *P. aeruginosa* ATCC27853	0.780	3.130	50.000	3.130
25. *P. aeruginosa* C4070	1.560	3.130	50.000	6.250

Table 1 (Continued)

Compound / Strain	Ex. 9	CTX	CPR	CAZ
1. *S. pyogenes* ATCC 8668	0.007	0.004	0.007	0.100
2. *S. pyogenes* C4003	0.007	0.004	0.007	0.200
3. *S. faecalis* ATCC 29212	> 100.000	> 100.000	50.000	> 100.000
4. *S. aureus* Smith	1.560	1.560	0.390	6.250
5. *S. aureus* ATCC 29213	1.560	1.560	0.780	6.250
6. *S. aureus* C4036	3.130	1.560	0.390	6.250
7. MRSA C2208	> 100.000	> 100.000	> 100.000	> 100.000
8. *S. epidermidis* ATCC12228	0.780	0.780	0.200	3.130
9. *E. coli* C4002	0.004	0.050	0.050	0.100
10. *E. coli* ATCC 10536	0.007	0.025	0.013	0.050
11. *E. coli* ATCC 25922	0.026	0.100	0.050	0.200
12. *E. cloacae* C4008	0.013	0.025	0.013	0.050
13. *E. cloacae* C4009	0.013	0.100	0.013	0.050
14. *K. oxytoca* C4022	1.560	0.780	1.560	0.780
15. *K. pneumoniae* C1040	0.004	0.025	0.025	0.050
16. *K. pneumoniae* ATCC 10031	0.002	0.002	0.013	0.050
17. *P. mirabilis* ATCC 25933	0.025	0.025	0.050	0.050
18. *P. rettgeri* ATCC 9919	0.004	0.004	0.013	0.025
19. *S. typhimurium* C4045	0.007	0.050	0.025	0.200
20. *S. marcescens* C1052	0.004	0.200	0.050	0.200
21. *S. marcescens* ATCC 27117	0.007	0.100	0.050	0.100
22. *P. aeruginosa* C2027	0.780	3.130	0.390	0.780
23. *P. aeruginosa* ATCC 10145	1.560	25.000	6.250	1.560
24. P. aeruginosa ATCC27853	0.780	25.000	3.130	3.130
25. *P. aeruginosa* C4070	3.130	50.000	6.250	1.560

Experiment 2: Pharmacokinetics (Plasma Half-Life)

In order to investigate the pharmacokinetics properties of the compounds according to the present invention, the plasma half-life was determined in accordance with the method described in Antimicrobial Agents and Chemotherapy, 26(2), p. 204-207 (1984).

In the experiment, the compound synthesized in Example 5 was selected as the test compound, and CAZ and CPR were used as reference compounds. The results are shown in Table 2 below.

Table 2

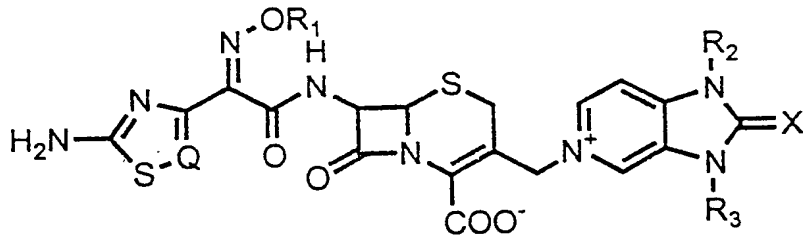
Compound	Half-Life ($T_{1/2}$, min)*	Remark
Ceftazidime (CAZ)	12.3	SD Rat
Cefpirome (CPR)	19.5	"
Compound of Example 5	24.0	"

* The half-life shows a mean value.

As can be seen from the foregoing, the compound of the present invention exhibits a significantly longer duration of action than any of the reference compounds.

CLAIMS

1. A cephem compound having the formula:



(I)

wherein, Q is a carbon or nitrogen atom; X is an oxygen atom, or a nitroalkyl or cyanoimine group, with the proviso that X cannot be an oxygen atom when Q is a carbon atom; R_1 is a hydrogen atom, or a lower alkyl group, or a lower alkyl group which may be substituted by fluoro, or by a carboxylic group or an inorganic cation salt thereof; and R_2 and R_3 independently are a hydrogen atom or a lower alkyl group; or pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein the compound of formula (I) is one of the following compounds:

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylenyl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2-(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate; and

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 94/00061

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: C 07 D 519/00, 501/46; A 61 K 31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 07 D 519/00, 501/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4 748 172 (A.S.KATNER) 31 May 1988 (31.05.88), claims 1-3; column 2, line 5 to column 3, line 50.	1,2
A	WO, A1, 92/22 556 (CHEIL FOODS & CHEMICALS, INC.), 23 December 1992 (23.12.92), claims 1-3.	1,2

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 1994 (18.08.94)	06 September 1994 (06.09.94)

Name and mailing address of the ISA/ AT	Authorized officer
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Facsimile No. 1/53424/535	Telephone No. 1/5337058/33

The expression "nitroalkyl" in line 12 of claim 1 should be corrected to "nitroalkylenyl" (see corrected abstract) and was read in this sense.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00061

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